New frontiers for management of hyperkalaemia: the emergence of novel agents

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Hyperkalaemia is a common electrolyte abnormality, associated with higher risk of morbid events, and increasing in prevalence—in part, due to increasing rates of comorbidities such as heart failure, chronic kidney disease, diabetes mellitus, and the use of renin-angiotensin-aldosterone system inhibitors (RAASIs). In spite of this growing problem, the existing treatments for chronic hyperkalaemia have been limited, and are typically confined to dietary potassium restrictions and cessation or modification of RAASIs, with latter option being potentially problematic given the known morbidity and mortality benefit of RAASI therapy in certain disease states, such as heart failure. The use of sodium polystyrene sulfonate (SPS/Kayexelate) for chronic hyperkalaemia has been low, due to poor tolerability, potential gastrointestinal safety concerns, and remaining uncertainty in regards to its efficacy. Given the shortcomings of existing therapies, novel treatments are clearly needed. There are now two novel treatment options, patiromer and sodium zirconium cyclosilicate (SZC), both approved by the FDA and EMA for treatment of chronic hyperkalaemia. These novel compounds have been demonstrated in multiple studies to be efficacious in achieving and maintaining normal serum potassium levels, over an extended time period, in patients with hyperkalaemia; and appear to be relatively safe and well-tolerated. Whether the correction of hyperkalaemia with these agents will allow optimization of RAASIs, which could theoretically lead to improvement in clinical outcomes, especially in patients with heart failure, remains to be determined. Several clinical trials are ongoing to address these important knowledge gaps.

Epidemiology of hyperkalaemia in patients with heart failure

Potassium is the most abundant intracellular cation in the human body. Potassium homoeostasis depends on adequate renal function but is also affected by comorbidities such as diabetes mellitus (DM) and heart failure (HF). Hyperkalaemia (serum potassium >5.0 mmol/L) is a common electrolyte abnormality with an increasing prevalence, in part due to the routine use of renin-angiotensin-aldosterone system inhibitors (RAASIs), such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), particularly when administered in combination. Numerous large observational studies have demonstrated a U shaped curve between serum potassium levels and adverse outcomes, including mortality. Further complicating the matter, the clinical benefits of RAASIs appear to be preserved in patients with HF with reduced ejection fraction even when these agents cause mild or moderate hyperkalaemia. Until recently, treatments for hyperkalaemia (especially in the outpatient setting) have been limited. Chronic hyperkalaemia has been primarily managed by dietary restrictions and cessation or modification of inciting agents, with alternative options being increased potassium excretion in the kidney through...
diuretic therapy, and potassium elimination in the GI tract with sodium polystyrene sulfonate (SPS/Kayexelate, Sanofi-Aventis, LLC, Bridgewater, NJ, USA).9 Despite widespread use for over four decades, the efficacy and safety of SPS remains controversial, as it was introduced in clinical practice prior to strict regulatory requirements for drug approval.9–11 Given the shortcomings of existing therapies and increasing prevalence of hyperkalaemia, novel treatments are clearly needed.

New treatments for hyperkalaemia

Two novel agents—patiromer (patiromersorbitex calcium/RLY5016; Veltassa; Relypsa, Red Wood City, CA, USA)12 and sodium zirconium cyclosilicate (SZC) (Lokelma; AstraZeneca PLC, 1 Francis Crick Avenue, Cambridge, UK)13 have recently emerged as promising potassium-lowering compounds. Both have now been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) and have data from well-conducted clinical trials demonstrating short- and long-term efficacy while being generally well tolerated. Here, we review the available clinical trial data on both patiromer and SZC.

Patiromer

Patiromer is a synthetic polymer consisting of non-absorbable spherical beads which exchange calcium for \( K^+ \) in the colon which is then excreted.14 Trials in healthy volunteers demonstrate a dose-related increase in stool \( K^+ \) excretion by 15–20 mmol, with an accompanying decrease in serum potassium levels within the target range. Phase 1 was 4 weeks open label initial treatment phase, where qualified patients were those with mild hyperkalaemia (5.1 to \( < 5.5 \) mmol/L) who received 4.2 g of patiromer b.i.d.; and those with moderate-to-severe hyperkalaemia (5.5 to \( < 6.5 \) mmol/L) who received 8.4 g of patiromer b.i.d., with doses being adjusted to achieve normokalaemia. The primary efficacy endpoint in the initial phase was mean change in the serum potassium level, which was \(-1.01 \pm 0.03\) mmol/L (\( P < 0.001 \)). By Week 4, 76% of patients in the initial treatment phase attained potassium levels within the target range. Phase 2 was 8 weeks placebo-controlled, single-blinded randomized withdrawal phase that consequently included patients with (i) baseline serum potassium levels of 5.5 to \( < 6.5 \) mmol/L during the screening for the initial phase and (ii) those who achieved target potassium levels between 3.8 and \( < 5.1 \) mmol/L, while receiving patiromer and RAASIs at the end of the initial phase. Patients were then randomly assigned in a 1:1 ratio to continue receiving patiromer or placebo for 8 weeks. At Week 8 of the randomized withdrawal phase, the recurrence of hyperkalaemia (potassium \( > 5.0 \) mmol/L) was observed in 43% (95% confidence interval (CI) 30–56%) of patients on patiromer when compared with 91% (95% CI 83–99%) on placebo (\( P < 0.001 \)). An exploratory analysis demonstrated that 94% of patients receiving patiromer were able to continue RAASI therapy by the end of the randomized phase compared with 44% of placebo-treated patients.

The Patiromer in the Treatment of Hyperkalaemia in Patients With Hypertension and Diabetic Nephropathy (AMEHYST-DN) study was performed to demonstrate the long-term safety and efficacy of patiromer in patients with mid-moderate hyperkalaemia (5.0–6.0 mmol/L) and diabetic kidney disease on RAASI therapy.15 In this multicentre,
open-label, single-arm, dose-ranging, and randomized trial patiromer was evaluated over 52 weeks period, consisting of 8 weeks initial treatment phase, 44 weeks maintenance phase, and 4 weeks post-treatment follow-up period. Participants in the study were adults with a diagnosis of Type 2 diabetes and CKD (eGFR 15–60 mL/min/1.73 m²) and had been treated with an ACEi, ARB, or both, for at least 28 days before screening. During the run-in period, initially normokalaemic patients were assigned into one of the two cohorts: in Cohort 1, baseline ACEi and/or ARB therapy was replaced with losartan 100 mg/day plus spironolactone 25 mg/day; in Cohort 2, patients were allowed to keep their current ACEi/ARB regimen with the addition of spironolactone 25 mg/day for blood pressure control; in both cohorts, spironolactone could be up-titrated if needed for blood pressure control. In these two cohorts, patients that developed hyperkalaemia at any time during run-in phase were eligible for randomization into the active treatment phase. A third cohort of patients was added to include eligible patients with pre-existing hyperkalaemia (serum potassium levels >5.0 to <6.0 mmol/L); these patients skipped the run-in and proceeded directly to randomized treatment phase. Following run-in, hyperkalaemic patients were randomly assigned to open-label patiromer at a starting dose of either 4.2 g, 8.4 g, and 12.6 g of patiromer twice daily for Stratum 1 (mild hyperkalaemia), and 8.4 g, 12.6 g, and 16.8 g of patiromer twice daily for Stratum 2 (moderate hyperkalaemia). Throughout the treatment and maintenance phases, patients continued RAASi therapy and the patiromer dose was titrated to achieve target serum potassium levels. The mean reduction in potassium from baseline to Week 4 of initial treatment phase ranged from –0.35 mmol/L to –0.97 mmol/L in a dose-dependent manner.

| Study | Trial population | Comparator groups | N | Study design | Follow-up (weeks) | Major finding |
|-------|------------------|------------------|---|--------------|-------------------|---------------|
| PEARL-HF | Chronic HF, CKD, or prior history of HK that led to stopping RAASi and indication to start spironolactone | Patiromer 15 g b.i.d. or placebo | 105 | Randomized and double blind. Patients started on 25 mg of spironolactone and titrated | 4 | Patiromer lowered serum K⁺ levels –0.45 mmol/L vs. placebo (P < 0.001) |
| OPAL-HK | eGFR (15-59 mL/min/1.73 m² and K⁺ 5.1-6.4 mmol/L) | Initial phase: cohort with mild HK (5.1-5.5 mmol/L) 4.2 BID i.e. 8.4 g per day. Cohort with moderate HK (5.6-5.9 mmol/L) 8.4 BID i.e. 16.8 g per day | 243 | Initial phase: single cohort and single blind | 4 | Mean K⁺ reduction –1.01 mmol/L |
| AMETHYST-DN | Type 2 DM, and eGFR (15-59 mL/min/1.73 m²) receiving RAASi. During run in period those that developed, mild or moderate HK enrolled. Patients with known HK allowed to skip run-in and proceed directly to randomized phase | Cohort with mild HK (5.1-5.5 mmol/L) 4.2 g, 8.4 g, or 12.6 g PO b.i.d. Cohort with moderate HK (5.6-5.9 mmol/L) 8.4 g, 12.6 g, or 16.8 g PO b.i.d. | 306 | Randomized and open label trial. Patients on baseline ACE-I or ARB, and started on spironolactone | 52 | Mild HK cohort: mean K⁺ reduction –0.35 mmol/L for 4.2 g, –0.51 mmol/L for 8.4 g, and –0.55 mmol/L for 12.6 g. Moderate HK cohort: mean K⁺ reduction –0.87 mmol/L for 8.4 g, –0.97 mmol/L for 12.6 g, and –0.92 mmol/L for 16.8 g. |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; K⁺, potassium; RAASi, renin-angiotensin-aldosterone system inhibitors.
(which in patients with HF and reduced systolic function may reduce CV death and hospitalizations). However, it should be noted that the number of patients with HF was overall limited in patiromer studies, and patients with more severe HF symptoms [New York Heart Association (NYHA) Class III or IV—which may especially benefit from optimal RAASI] were excluded. Additionally, PEARL-HF used a vague definition of chronic HF and inclusion was based largely upon the investigators clinical judgement. A meta-analysis of patiromer studies showed a reduction in serum potassium of −0.36 mmol/L at 3 days and −0.70 mmol/L (95% CI −0.48 to −0.91 mmol/L; n = 603) in 4 weeks. The meta-analysis also found that 74–95% of patients were maintained in the normal potassium range long term; 93% of patients were able to maintain, initiate, or titrate RAASI during maintenance phases of the studies.

**Adverse events/safety**

The most common adverse effects of patiromer are GI related. In the pooled dataset, treatment-related adverse events occurred in 54% of the patiromer group and 31% of the placebo group. GI symptoms occurred in 21% of the patiromer group and 6% of the placebo group. The most common adverse events noted were flatulence, diarrhoea, constipation, and vomiting. Discontinuation of therapy due to an adverse effect occurred in 8% (43/538) of patients on patiromer. Patiromer may bind divalent cations, in addition to potassium, and hypomagnesaemia has been seen in all three clinical trials. In PEARL-HF, hypomagnesaemia was defined as serum magnesium level <1.8 mg/dL during the treatment period and was seen in 13 (24%) patiromer-treated patients vs. 1 (2.1%) placebo-treated patient (more severe hypomagnesaemia was not reported). In OPAL-HK, eight patients (3%) had serum magnesium <1.4 mg/dL, but none had magnesium <1.2 mg/dL. During AMETHYST-DM, 13 patients (4.3%) had magnesium <1.2 mg/dL, but none had magnesium <1.0 mg/dL. In a meta-analysis of patiromer studies, hypokalaemia occurred in 3% of patients during the 28 days follow-up and 5.6% over 52 weeks follow-up, and was generally mild. During AMETHYST-DM, 13 patients (4.3%) had hypokalaemia (serum potassium 4.6–6.0 mmol/L) were randomized to escalating doses of SZC (0.3 g, 3 g, or 10 g) or placebo, administered three times daily (Table 2). Sodium zirconium cyclosilicate significantly reduced serum potassium from baseline, with a mean reduction of 0.92 mmol/L at 38 h in the 10 g dose group, compared with 0.26 mmol/L with placebo (P < 0.001). In addition, 41.7% of patients on 10 g SZC vs. 3.4% on placebo had a >1.0 mmol/L reduction in serum potassium, which was maintained for 3.5 days after the last dose of SZC. Packham et al., conducted the first Phase III study of SZC for hyperkalaemia in a 754 patients who had a documented serum potassium level of 5.0–6.5 mmol/L. Nearly 75% of patients had CKD, 60% had T2DM, 40% had history of HF, and 67% of patients were receiving RAASI. The trial was divided into two parts, an initiation phase and a maintenance phase. In the initial phase, patients were randomly assigned to receive either placebo (158 patients) or SZC at a dose of 1.25 g (154 patients), 2.5 g (141 patients), 5 g (157 patients), or 10 g (143 patients) three times/day with meals for 48 h. The primary endpoint for the initial phase was the exponential rate of change in mean serum potassium level during the first 48 h of treatment. After the initial 48 h, SZC treatment produced a statically significant and dose dependent reduction in serum potassium levels of −0.3 mmol/L, −0.5 mmol/L, −0.7 mmol/L, and −0.7 mmol/L for the 1.25 g, 2.5 g, 5 g, and 10 g groups (vs. 0.3 mmol/L with placebo). The decline in the potassium level was rapid and dose-dependent and most pronounced in patients with the highest potassium levels at baseline. The effects of SZC were consistent across various subgroups, including patients with HF, CKD and diabetes, and across various degrees of hyperkalaemia at baseline. In patients who received 5 g of SZC and those who received 10 g of SZC, serum potassium levels were maintained at 4.7 mmol/L and 4.5 mmol/L, respectively, during the 12 days maintenance phase, when compared with a level of more than 5.0 mmol/L in the placebo group (P < 0.01 for all comparisons).

**Sodium zirconium cyclosilicate**

**Structure and MOA**

Sodium zirconium cyclosilicate is an odourless, tasteless powder formulated for oral use, mixed with water to form a suspension, and given with food in completed clinical trials. Unlike other potassium binders, SZC is an inorganic crystal, not an exchange resin. Sodium zirconium cyclosilicate’s site of action is thought to be within the entire gastrointestinal tract where it binds potassium in exchange for sodium or hydrogen cations, and facilitates potassium excretion in the faeces. Sodium zirconium cyclosilicate has a three-dimensional crystalline lattice structure composed of zirconium, silicon, and oxygen that are arranged to form cation-binding pores. It was designed with a binding pore that preferentially traps potassium ions due to its 3 angstrom (Å) pocket size, as potassium’s unhydrated diameter is approximately 2.98 Å. As such, SZC possesses high selectivity for K+ ions, considerably greater than that of SPS and does not bind calcium or magnesium. Because of its high selectivity for potassium, it is believed to exert a pharmacologic effect soon after ingestion as it moves throughout the digestive tract. Sodium zirconium cyclosilicate is excreted in the faeces and it is not systemically absorbed.
The study included the initial open-label 48 h in-
outpatients with hyperkalaemia for up to
The HARMONIZE trial investigated the efficacy and safety
HARMONIZE trial
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L or higher were documented, with the majority of patients
inclusion if two consecutive potassium levels of 5.1 mmol/

patients by 24 h and 98% (95% CI 96–99%) of patients by

maintenance phase. Patients were considered eligible for study
inclusion if two consecutive potassium levels of 5.1 mmol/L
or higher were documented, with the majority of patients
having CKD or history of HF. A total of 70% of study partici-
pants were prescribed RAASis at baseline. The mean base-
line serum potassium level was 5.6 mmol/L. Patients
(n = 258) were treated with SZC (10 g three times daily) in
the 48 h open-label phase; those achieving normokalaemia
(potassium 3.5–5.0 mmol/L; n = 237) were randomized to
receive three different SZC doses or matching placebo for
28 days.

In the initial 48 h open-label induction phase, statistically
significant reduction in serum potassium from baseline
(−0.2 mmol/L) was observed at 1 h after the first 10 g dose of
SZ. Absolute change in serum potassium was −0.7 mmol/
L (95% CI −0.7 to −0.6) at 24 h and −1.1 mmol/L (95% CI
−1.1 to −1.0) at 48 h. Normokalaemia (serum potassium

HK, hyperkalaemia; K⁺, potassium; RAASi, renin-angiotensin-aldosterone system inhibitors.

HARMONIZE trial
The HARMONIZE trial investigated the efficacy and safety
of SZC in outpatients with hyperkalaemia for up to 4
weeks. The study included the initial open-label 48 h in-
duction phase, followed by a 28 day randomized mainte-
nance phase. Patients were considered eligible for study
inclusion if two consecutive potassium levels of 5.1 mmol/L
or higher were documented, with the majority of patients
having CKD or history of HF. A total of 70% of study particip-
ants were prescribed RAASis at baseline. The mean base-
line serum potassium level was 5.6 mmol/L. Patients
(n = 258) were treated with SZC (10 g three times daily) in
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Table 2 Summary of SZC clinical trial data

| Study   | Trial population | Comparator groups | N  | Study design              | Follow-up | Major finding                                      |
|---------|------------------|-------------------|----|---------------------------|-----------|---------------------------------------------------|
| ZS-002  | Stable CKD (eGFR 30-60 mL/min/1.73 m²) and mild to moderate HK (5.1-5.9 mmol/L) | SZC 0.3 g, 3 g, or 10 g vs. placebo | 90 | Randomized, double blind, and placebo-controlled | 48 h      | SZC had a 0.92 mmol/L mean reduction of serum K⁺ at 38 h in the 10 g dose group, comparing 0.26 mmol/L with placebo (P < 0.001). |
| ZS-003  | Initial phase serum K⁺ 5.0-6.5 mmol/L | SZC 1.25 g, 2.5 g, 5 g, or 10 g or placebo three times daily | 753 | Initial phase: double blind and placebo controlled | 48 h      | SZC had a mean serum K⁺ reduction of −0.3 mmol/L, −0.5 mmol/L, −0.7 mmol/L, and −0.9 mmol/L for the 1.25 g, 2.5 g, 5 g, and 10 g groups, respectively (vs. −0.3 mmol/L with placebo) |
|         |                  | Maintenance phase: those who achieved serum K⁺ 3.5-4.9 mmol/L at 48 h |     | Maintenance phase: continued on same dose of SZC or switched to placebo | 12 days   | 5 g and 10 g of SZC maintained serum K⁺ at 4.7 mmol/L and 4.5 mmol/L, respectively, when compared with a level of more than 5.0 mmol/L in the placebo group (P < 0.01 for all) |
|         |                  | Maintenance phase: those who achieved serum K⁺ 3.5-5.0 mmol/L at 48 h |     | Maintenance: randomized, double-blind, and placebo controlled | 28 days   | Normokalaemia (3.5-4.9 mmol/L) was achieved in 84% at 24 h and 98% at 48 h. |
|         |                  | Maintenance phase: those who achieved serum K⁺ 3.5-5.0 mmol/L at 48 h |     | Maintenance: randomized, double-blind, and placebo controlled |           | Normokalaemia (3.5-5.0 mmol/L) was maintained in 80%, 90%, 94%, and 46% of patients in the 5 g, 10 g, 15 g, and placebo groups, respectively vs. placebo (P < 0.001). |

HZS-002 Stable CKD (eGFR 30-60 mL/min/1.73 m²) and mild to moderate HK (5.1-5.9 mmol/L) was achieved in 84% (95% CI 79-88%) of patients by 24 h and 98% (95% CI 96-99%) of patients by 48 h. Median time to potassium normalization was 2.2 h (interquartile range 1.0-22.3).

Patients who achieved normokalaemia in the initial phase were then randomized to receive SZC, 5 g (45 patients), 10 g (51 patients), 15 g (56 patients), or placebo (85 patients) once/day for a total of 28 days. Serum potassium during days 8-29 was significantly reduced in all SZC groups vs. placebo, with numerically lower potassium levels in the placebo group (P < 0.001). This effect was consistent throughout the randomized phase. Normokalaemia was maintained in 80%, 90%, 94%, and 46% of patients in the 5 g, 10 g, 15 g, and placebo groups (P < 0.001). The potassium-lowering effect of SZC was consistent across all patient subgroups.

A pooled analysis of three Phase II and III SZC trials demonstrated a mean change in potassium at 48 h was −0.67 mmol/L (95% CI −0.45 to −0.89; n = 760).
Subgroup analysis of patients with HF, the mean change in potassium at 48h was −1.2 mmol/L following SZC dosed at 10 g three times daily. Change in potassium at 1 h was −0.17 mmol/L (95% CI −0.05 to −0.30 mmol/L). Pooled analysis of those with severe hyperkalaemia noted even more rapid decrease in serum potassium after a single 10 g dose of SZC. In the total cohort of the combined studies, 45 patients had a baseline serum potassium level of at least 6.0 mmol/L (range 6.1–7.2) and received a 10 g dose of SZC. The mean serum potassium level at baseline was 6.3 mmol/L (95% CI 6.2–6.4). After one 10 g dose of SZC, the mean serum potassium level declined by 0.4 mmol/L (95% CI 0.2–0.5) at 1 h, by 0.6 mmol/L (95% CI 0.4–0.8) at 2 h, and by 0.7 mmol/L (95% CI 0.6–0.9) at 4 h (P < 0.001 for the comparison of each time point with baseline). The median time to a serum potassium level <6.0 mmol/L was 1.07 h, and the median time to a level that ≤5.5 mmol/L was 4 h. By 4 h, 80% of the patients had a serum potassium level that was less than 6.0 mmol/L, and 52% had a level that was 5.5 mmol/L or less. A dedicated trial using SZC for those with moderate to severe hyperkalaemia in the emergency room setting is currently ongoing (clinicaltrials.gov NCT03337477).

Multiple studies have demonstrated that SZC is effective both in rapidly lowering potassium to normal range and maintaining normal potassium levels for up to 4 weeks. A large, 1 year open-label study of SZC investigating efficacy and safety for up to 1 year has been completed, and the results are pending (Clinicaltrials.gov NCT02163499).

Likewise, longer-term trials of SZC in patients with hyperkalaemia on dialysis (Clinicaltrials.gov NCT03303521) and HF with reduced systolic function on suboptimal RAASIs (NCT03303521) are ongoing.

Adverse events/safety

In the HARMONIZE trial, treatment-related AEs, including gastrointestinal AEs, were comparable across the groups. Oedema was observed more frequently with 15 g SZC dose than with the other doses of SZC or with placebo. It is possible that higher oedema rates may be related to the higher sodium content in 15 g of SZC; however, there were no significant changes in blood pressure, or body weight at any dose level, and no dose-dependent increase in urinary sodium excretion was noted. This difference might also be partially explained by significantly higher baseline rates of HF and eGFR less than 60 mL/min/1.73 m² and higher baseline levels of brain natriuretic peptide among patients receiving 15 g dose of SZC vs. placebo. There was a numerically higher rate of hyperkalaemia with higher SZC doses; all episodes of hypokalaemia were mild. No significant drug-drug interactions were identified to date.

Conclusion

Until recently, the treatment of hyperkalaemia has remained unchanged since the 1950s, with several available treatment options lacking clear evidence of efficacy, and/or exhibiting significant tolerability issues and safety concerns. There are now two novel agents, patiromer and SZC, both of which have been approved by the FDA and EMA for treatment of chronic hyperkalaemia. These novel compounds have been demonstrated to be efficacious in achieving and maintaining normal serum potassium levels in patients with hyperkalaemia, and generally appear to be well tolerated.

Several critically important questions remain in regard to these agents. First, their use has so far been limited to outpatients with hyperkalaemia. Whether they can be successfully used for acute management of hyperkalaemia in the Emergency Department or on hospital wards remains unclear, and will require confirmation in future studies that include acutely ill patients. The use of these agents in patients with end stage renal disease has also not been evaluated, and remains an important knowledge gap, as patients with ESRD require chronic hyperkalaemia management more than any other group. Finally, it remains to be seen whether or not the correction of hyperkalaemia with these agents will allow optimization of RAASI in patients with HF and reduced left ventricular ejection fraction in a safe fashion; and, furthermore, whether this optimization of RAASI will result in better clinical outcomes. Several clinical trials are currently ongoing to address some of these clinically important knowledge gaps.

Conflict of interest: MN: Honoraria Abbott Medical. MK: advisory boards for AstraZeneca, Boehringer Ingelheim, Sanofi, Glytec, NovoNordisk, ZSPharma, GSK, Amgen, Eisai, Merck (Diabetes); consultant for AstraZeneca, Sanofi, and ZS Pharma, research grants from AstraZeneca and Boehringer Ingelheim.

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