Can an implanted minipump deliver for diabetes patients?

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The FREEDOM studies evaluated exenatide delivered via an implanted minipump in patients with type 2 diabetes; the final study evaluated cardiovascular outcomes but offers up more questions than answers.

Glucagon-like peptide-1 (GLP-1) receptor agonists are used to treat patients with type 2 diabetes (T2D); as well as improving glycemic control, some have been shown to reduce cardiovascular events in these patients[1]. One agent in this class — exenatide — is currently available in two formulations, for subcutaneous injection either twice daily or once weekly[2]. There were concerns that such regimens might be inconvenient and that adherence might be suboptimal; therefore, a drug–device combination (named ITCA 650) was developed for continuous subcutaneous infusion of exenatide using an implanted osmotic minipump[3,4,5,6,7,8]. In this issue of *Nature Medicine*, Ruff et al.[9] present results of the FREEDOM cardiovascular outcomes (FREEDOM-CVO) trial, which evaluated ITCA 650 and cardiovascular outcomes in patients with T2D. This long-awaited trial builds on a sequence of smaller, shorter-term studies that evaluated the practicalities and acceptability of the ITCA 650 device—which requires a minor surgical procedure—as well as biomarker evidence of effective and sustained delivery of exenatide.

The weekly formulation was initially studied in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, in which a subcutaneous dose of 2 mg per week was compared to placebo in 14,752 patients with T2D, most of whom had cardiovascular disease[2]. Over a median duration of 3.2 years of follow-up, there was no reduction in the primary three-component composite outcome of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke (Table 1). The lack of efficacy in reducing cardiovascular outcomes was disappointing, given the favorable effects of other agents in this class, although the striking 43% rate of premature discontinuation of the study drug may have attenuated any potential treatment benefit. Consequently, the results of the FREEDOM-CVO, the last and largest of a series of trials in the FREEDOM program[3,4,5,6,7,8], have been eagerly awaited as exenatide (in the same formulation used in EXSCEL) was delivered by ICTA 650 continuous subcutaneous infusion[9].

Table 1 Comparison of outcomes in FREEDOM-CVO and EXSCEL

	FREEDOM-CVO			EXSCEL		
	Exenatide (*n* = 2,075)	**Placebo (*n* = 2,081)**	**HR (95% CI)**	**Exenatide (*n* = 7,356)**	**Placebo (*n* = 7,396)**	**HR (95%CI)**
Cardiovascular outcomes, number (rate per 100 person-year)						
Cardiovascular death, myocardial infarction, stroke[a]	85 (2.9)	69 (2.4)	1.24 (0.90,1.70)	839 (3.7)	905 (4.0)	0.91 (0.83,1.00)
Cardiovascular death	28 (1.0)	23 (0.8)	1.22 (0.70,2.12)	340 (1.4)	383 (1.5)	0.88 (0.76,1.02)
All-cause death	49 (1.7)	41 (1.4)	1.20 (0.79, 1.81)	507 (2.0)	584 (2.3)	0.86 (0.77, 0.97)
Other outcomes						
Change in glycated hemoglobin level[b]	–0.84% (–0.98, –0.70)		–	–0.53% (–0.57, –0.50)		–
Change in weight[b]	–4.24 kg (–4.82, –3.65)		–	–1.27 kg[c]		–
New glucose-lowering treatment	–		HR 0.48 (0.41, 0.55)	–		HR 0.67 (0.63, 0.71)
New insulin treatment	13.7%	6.7%	–	13.8%	9.4%	–

CI, confidence interval; HR, hazard ratio. aPrimary endpoint in EXSCEL and key secondary outcome in FREEDOM-CVO. The primary outcome in FREEDOM-CVO was a four-component composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina: outcome observed in in 95 patients in exenatide arm and 79 patients in the placebo arm (HR 1.21, 95% CI 0.90, 1.63; P = 0.004 for non-inferiority). bPlacebo-corrected change over duration of trial (95% CI). c95% CI not provided.

In FREEDOM-CVO, study devices were placed subdermally in the abdomen under local anesthesia, a procedure that requires a 5-mm skin incision. Patients were randomly assigned to ITCA 650 or placebo; those in the ITCA 650 group received 20 µg per day for 3 months after which this was replaced with ITCA 650 60 µg per day for 6 months. This was then replaced with a new device (same dosage) every 6 months thereafter until the end of the trial, at which time the device was permanently removed. People assigned to the placebo group received matching devices without exenatide.

Unfortunately, FREEDOM-CVO was a much smaller trial than EXSCEL, with shorter follow-up and far fewer events[2,9]. It was not powered for superiority, although non-inferiority was demonstrated for the primary four-component composite cardiovascular outcome[9]. At first glance, the unfavorable point estimates for the hazard ratios for cardiovascular outcomes (all >1) may raise questions about the safety of the treatment. However, assuming the exenatide exposure during FREEDOM-CVO was similar to that obtained with weekly injections of exenatide in EXSCEL, then it is the latter trial that provides a far more robust estimate of the true effect of this agent on cardiovascular events. In EXSCEL, 11 times as many people experienced the three-component composite cardiovascular outcome as in FREEDOM-CVO (Table 1). Therefore, the lack of conclusive evidence for the efficacy of exenatide on cardiovascular outcomes remains a disappointment given the clear cardiovascular benefits of other agents in this class[1]. Moreover, and surprisingly, adherence seemed to be only slightly better in FREEDOM-CVO than in EXSCEL, when the different durations of follow-up are taken into account: 43% of patients discontinued exenatide over a median follow-up of 3.2 years in EXSCEL compared with 17.6% over a median follow-up of 1.3 years in FREEDOM-CVO[2,9].

The biochemical and other surrogate outcomes provide more insight, although these were exploratory endpoints and cross-trial comparisons are always tentative[2,9]. While the different durations of follow-up also make this comparison difficult, the placebo-corrected reduction in glycated hemoglobin with exenatide was substantially greater, overall, in FREEDOM-CVO than in EXSCEL, even over the first 6 months of treatment in EXSCEL (when adherence was best; Table 1). Although the placebo-corrected reduction in weight with exenatide in FREEDOM-CVO was substantial compared to EXSCEL, similar or even larger weight reductions can be achieved with other GLP-1 RAs[10].

What are the potential downsides of this new therapeutic approach? Anti-exenatide antibodies were found in 16.9% of patients treated with exenatide compared with 0.7% of patients in the placebo group ($P < 0.0001$), although these were reported to be predominantly of low titer, and their clinical significance is uncertain[9]. Surprisingly, ‘acute renal failure events’ occurred in 39 patients (1.9%) in the ITCA group and 24 patients (1.2%) in the placebo group ($P = 0.06$); the slightly higher rate in the ITCA group could be related to gastrointestinal disturbances, which can be induced by GLP-1 receptor agonist. No adverse events related to the implantation of the device were reported, although in an earlier study, bruises at the site of implantation, mild bleeding and minor pain occurred at an incidence of 3.9–4.6%. The incidence of superficial skin infection in that earlier study was low (1.3%)[6,7].

The technology evaluated offered the possibility of a matchstick-sized osmotic minipump inserted just beneath the skin to provide consistent delivery of medication for 6 months or longer, removing the need for weekly or monthly injections. However, the challenge is the safe manufacturing of a mechanically reliable device that consistently delivers the drug of interest and fulfils the high standards of performance required by regulators. It remains to be seen whether the ITCA 650 will meet this high bar[11].

FREEDOM-CVO was a well-conducted trial with innovative technology; however, the evidence showing a reduction in cardiovascular events is stronger for other GLP-1 RAs than for exenatide. Even if the device can be manufactured to the exacting standards required, will primary care physicians and endocrinologists be willing to undertake the procedure? Will patients be prepared to accept the small risk of local complications? Although improvement in adherence was a major driver in the development of this approach, it is not clear that adherence was substantially better with ITCA 650 than with weekly exenatide. The potential cost of the device is not public, and any benefits justifying a greater cost than that for conventional GLP-1 receptor agonist therapy are unclear; therefore, the future of this approach remains uncertain.

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Competing interests

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