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Use of EMPAgliflozin in the prevention of CARDiotoxicity: the EMPACARD – PILOT trial

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Abstract

Background Anthracycline-based chemotherapy represents a cornerstone treatment for a number of common cancers, including breast cancer, lymphoma, and sarcoma. However, anthracycline-induced cardiotoxicity remains a significant concern, often presenting as a decline in cardiac function which can ultimately lead to heart failure (HF) or asymptomatic left ventricular dysfunction, in up to 10–15% of patients.Sodium-glucose transport protein 2 inhibitor (SGLT2i) therapies have been demonstrated to reduce the incidence of HF in high-risk non-cancer patients. Preliminary retrospective data suggest their role in mitigating the incidence of HF during or after anthracycline treatment

Methods The EMPACARD-PILOT trial was a prospective case–control study involving breast cancer patients scheduled to undergo anthracycline-based chemotherapy in a 4-cycle protocol of 60 mg/m2 doxorubicin. We used the HFA/ICOS risk score to identify patients at high or very high risk of cardiotoxicity. Patients with diabetes mellitus or stable heart failure with preserved ejection fraction (HFpEF) were prescribed empagliflozin (10 mg per day), starting seven days before the administration of anthracyclines and continuing for a period of six months. Those not meeting these criteria served as controls. The primary endpoint was cancer therapy-related cardiac dysfunction (CTRCD) incidence. CTRCD was defined as either a decrease in left ventricular ejection fraction (LVEF) of at least 10% to a final value below 50% or a reduction in global longitudinal strain (GLS) of at least 15% from baseline at any point during the study. The secondary endpoints included mortality and hospitalization due to cardiovascular causes or clinical heart failure. Exploratory endpoints included increases in serum troponin and NT-proBNP levels and a decrease in the glomerular filtration rate (GFR). The safety endpoints tracked includedketoacidosis, hypoglycemia, sepsis, neutropenic fever, and urinary tract infections.

Results During the enrollment period, 785 breast cancer patients were analysed. Of these, 107 met the inclusion criteria, and 76 subsequently provided informed consent. The study was conducted with comparable adherence rates of 81.5% in both the empagliflozin group ($n=38$) and the control group ($n=38$). The follow-up data from 62 patients revealed a significant reduction in the primary outcome within 6 months for the empagliflozin group compared with the control group (6.5% vs. 35.5%, $p=0.005$), with a relative risk of 0.18 (95% CI: 0.04–0.75). Compared with the control treatment, treatment with empagliflozin also significantly preserved the ejection fraction at 6 months follow-up (56.8% ± 5.8% vs. 53.7% ± 6.7, $p=0.029$). However, there were no significant differences between the groups in terms of NT-proBNP, cTnI, clinical heart failure, GFR, or mortality/hospitalization due to heart failure.

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Conclusion Empagliflozin is associated with reduced incidence of CTRCD in high-risk patients treated with anthracyclines. These data should serve as the foundation for a clinical trial to test whether SGLT2 inhibitors can reduce the incidence of heart failure in this patient group.

Background

Anthracycline-based chemotherapy is the standard treatment for several common cancer types, such as breast cancer, lymphoma, and sarcoma [1]. However, the use of anthracyclines is associated with the potential for the development of cardiac toxicity [2, 3]. Anthracyclines can cause cardiac toxicity, which often results in a reduction in cardiac function and can lead to heart failure (HF). HF incidence has been reported in up to 10–15% of these patients [4]. Currently, there are no established therapies to attenuate or prevent the development of anthracycline-induced cardiotoxicity (AIC) and reduce the risk of HF. Sodium–glucose transport protein 2 inhibitor (SGLT2i) therapies can reduce the incidence of HF in high-risk patients who have received anthracyclines [5, 6]. Strong scientific plausibility and preliminary data suggest that SGLT2i may also reduce the incidence of HF in those with AIC.

Anthracyclines are known to increase cytokines, reduce cardiomyocyte viability, and lead to cardiomyocyte apoptosis and myocardial fibrosis, all of which contribute to their cardiotoxicity [7]. Myocardial fibrosis plays a crucial role in the progression from cardiotoxicity to clinical heart failure [7]. In patients not treated with anthracyclines, the protective benefits of SGLT2i are postulated to include a reduction in pathologic cytokines and improved cell viability, leading to decreased cardiomyocyte apoptosis and myocardial fibrosis. In animal models of anthracycline cardiotoxicity, SGLT2i prevented the increase in cytokines, as well as the reduction in cardiomyocyte viability, the increase in cardiomyocyte apoptosis, and myocardial fibrosis [8, 9].

Retrospective data support our hypothesis that SGLT2i may improve cardiac outcomes when used with anthracyclines. Several retrospective studies have shown that SGLT2i reduces heart failure hospitalizations [10] and the composite primary cardiac outcome of cardiac events, including heart failure incidence, heart failure admissions, new cardiomyopathy (defined as a > 10% decline in the ejection fraction to < 53%), and clinically significant arrhythmias [11].

Therefore, we conducted a prospective case–control study to examine the impact of SGLT2 inhibitors on cardiac dysfunction in patients with diabetes mellitus receiving anthracycline treatment.

Methods

The EMPACARD–PILOT trial was a prospective case–control study. We included breast cancer patients scheduled to undergo a 4-cycle protocol of doxorubicin at 60 mg/m2. The study specifically targeted a population at high or very high risk of cardiac toxicity, as determined by the HFA/ICOS risk score [12]. Patients were excluded if they had a left ventricular ejection fraction (LVEF) < 50% at baseline; prior HF hospitalization; or myocardial infarction, coronary revascularization, stroke, or transient ischaemic attack within 90 days of the start of the study. Additional exclusion criteria included previous use of SGLT2i, systolic BP ≥ 180 mmHg or diastolic BP > 100 mmHg, severe kidney dysfunction with an estimated GFR of < 20 ml/min/m^2, a history of ketoacidosis, a known allergy to SGLT2i, or pregnancy. All enrolled patients provided signed informed consent.

Study intervention

After screening and providing consent, patients with diabetes mellitus or stable HFpEF were assigned to the Empagliflozin arm (10 mg per day), whereas the other patients were placed in the control group. The study drug was started 7 days before the anthracyclines were taken and continued for 6 months. Patients were evaluated at baseline, before the second and fourth cycles of chemotherapy, and 3 months post chemotherapy (6-month follow-up). Each study visit included a review of symptoms, serum biomarkers, an echocardiogram to assess LVEF and GLS, and the recording of study-related adverse events. Patients who failed to attend evaluations or did not adhere to daily medication were withdrawn from the study.

Study endpoints

The primary study endpoint, cancer therapy-related cardiac dysfunction (CTRCD), was defined as a decrease in LVEF of at least 10% from baseline to a final LVEF of less than 50% and/or a relative decrease of at least 15% in global longitudinal strain (GLS) from baseline at any time in the study. The secondary endpoint was a clinical endpoint and was a composite of death or hospitalization due to CV causes and/or clinical heart failure. Incident heart failure was defined by the European Society of Cardiology [ESC] [13]. Exploratory endpoints included an increase in serum troponin, an increase in NT-proBNP, and a decrease in the GFR. The safety endpoints were the occurrence of ketoacidosis, hypoglycemia, sepsis, neutropenic fever, or urinary tract infection.

Statistical methods

Categorical variables are presented as absolute and relative frequencies and were compared with the chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as the means with standard deviations and were compared with Welch's t test. Statistical significance was set at $p < 0.05$. All calculations were performed with R version 4.3.0. We determined that the sample size would be 100 patients in each arm.

Results

A total of 785 patients with breast cancer were analysed, with 107 meeting the inclusion criteria. Of these, 76 women consented to participate and signed the informed consent form. Thirty-eight patients were assigned to the Empagliflozin arm, and 38 were assigned to the Control arm (Fig. 1). The adherence rate was 81.5% in both arms. There were no significant differences in baseline characteristics between adherent and nonadherent patients (Supplementary Table S1). All study participants were women treated for breast cancer, with a high prevalence of cardiovascular risk factors. Most participants were at stage III, and 23.68% had previously been treated with doxorubicin, with an average mean doxorubicin dose of

310,26 mg/m^2 (Table 1). A follow-up was available for 62 patients.

Primary outcome

Within 6 months, the primary outcome occurred in 35.5% of the participants in the control group and in 6.5% of those in the empagliflozin group ($p = 0.005$, Figs. 2). Compared with the control group, the empagliflozin group presented significant preservation of LVEF (56.8% ± 5.8 versus 53.7% ± 6.7, $p = 0.029$) Figs 3. Compared with the control group, the empagliflozin group had a relative risk of 0.18 for the primary outcome, with a 95% CI of 0.04 to 0.75, indicating a reduced risk of decline in LVEF. Additionally, the empagliflozin group exhibited significant preservation of GLS compared with the control group (5.3% vs. 32%, $p = 0.003$). The only significant difference between the placebo and treatment groups in terms of basal characteristics was the use of beta-blockers (58% in the Empagliflozin group and 34% in the placebo group, $p = 0.038$). When adjusting for beta-blocker use, the protective effect of empagliflozin remained significant, with an OR for the primary endpoint for the placebo group of 10.29 ± 2.48 ($p = 0.0055$).
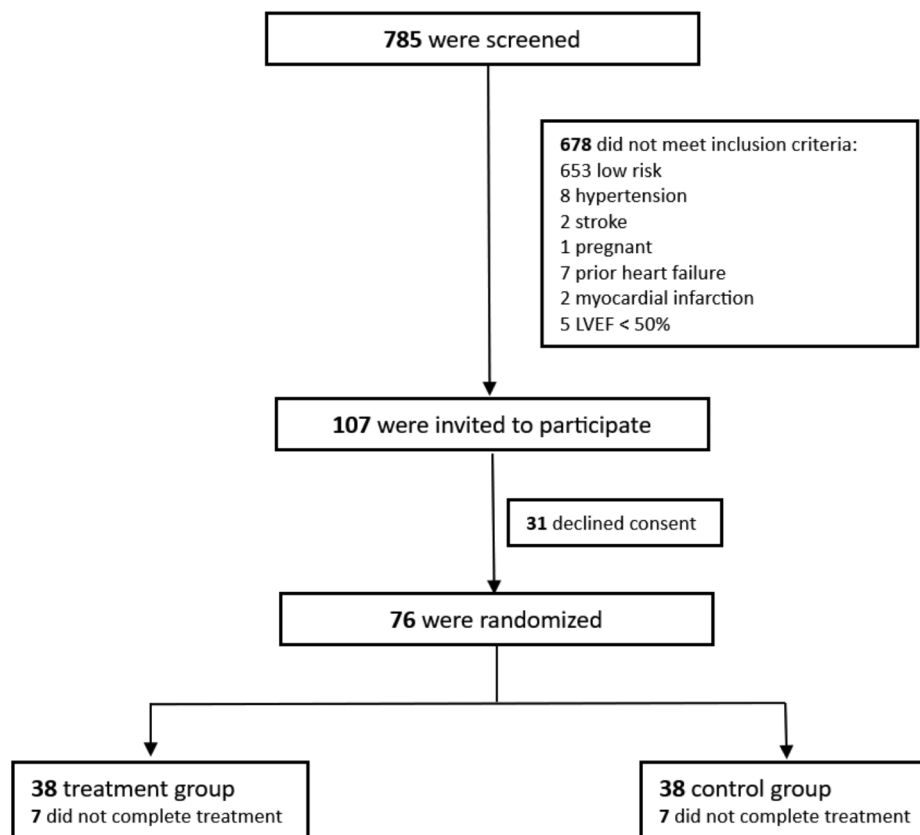

Fig. 1 Screening and follow-up

Table 1 Baseline characteristics

Characteristic	Empagliflozin, N=38[1]	Placebo, N=38[1]	*p*-value
Age	68 (9.2)	68.5 (9.6)	>0.9
Cardiovascular risk factors			
Hypertension	36 (95%)	37 (97%)	>0.9
Diabetes	33 (87%)	31 (82%)	0.5
Smoker or former smoker	19 (50%)	24 (63%)	0.2
Obesity	15 (39%)	20 (53%)	0.2
Cardiovascular disease			
Heart failure	3 (7.9%)	3 (7.9%)	>0.9
Valvular heart disease	2 (5.3%)	2 (5.3%)	>0.9
Myocardial infarction or revascularization	4 (11%)	4 (11%)	>0.9
Basal ejection fraction	59.3 (4.7)	58.3 (4.7)	0.6
Basal NYHA functional class			0.2
I	10 (59%)	13 (100%)	
II	7 (41%)	0 (0%)	
III	0 (0%)	0 (0%)	
IV	0 (0%)	0 (0%)	
Basal ejection fraction 50–54%	10 (26%)	8 (21%)	0.6
GFR 20–60 ml/min/m2	7 (18%)	9 (24%)	0.6
Increased basal troponin	1 (2.6%)	0 (0%)	>0.9
Increased basal NT-proBNP	5 (13%)	5 (13%)	>0.9
Cardiovascular medications			
ACE inhibitors	37 (97%)	38 (100%)	>0.9
Statins	25 (66%)	30 (79%)	0.2
Beta-blockers	22 (58%)	13 (34%)	0.038
Aspirin	5 (13%)	2 (5.3%)	0.4
Diuretics	6 (16%)	5 (13%)	0.7
Cancer characteristics and treatment			
Breast cancer stage			0.7
IIIA	17 (45%)	15 (39%)	
IIIB	8 (21%)	11 (29%)	
IIIC	5 (13%)	7 (18%)	
IV	8 (21%)	5 (13%)	
HER2 positivity (%)	67 (9)	66 (10)	>0.9
Prior doxorubicin treatment	10 (26%)	9 (24%)	0.8
Prior radiotherapy	10 (26%)	8 (21%)	0.6
Prior chemotherapy without doxorubicin	8 (21%)	10 (26%)	0.6
Doxorubicin dose in mg/m^2			>0.9
180	0 (0%)	1 (2.6%)	
240	38 (100%)	37 (97%)	
Cumulative doxorubicin dose	317 (137)	303 (123)	>0.9

[1] Mean (SD); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum exact test

Secondary outcomes

There was no significant difference between the two groups in terms of clinical heart failure, death, or hospitalization due to heart failure (Table 2).

Exploratory endpoints

NT-proBNP elevation, cTnI elevation, and GFR decrease were not significantly different between the two groups (Table 2).

Safety outcomes

There was a low overall incidence of adverse effects, with no significant difference between the groups, as shown in Table 3.

Discussion

Heart failure and cancer are intricately linked pathologies. Research has demonstrated that the presence of heart failure in patients is a risk factor for developing cancer [14]. On the other hand, advances in cancer
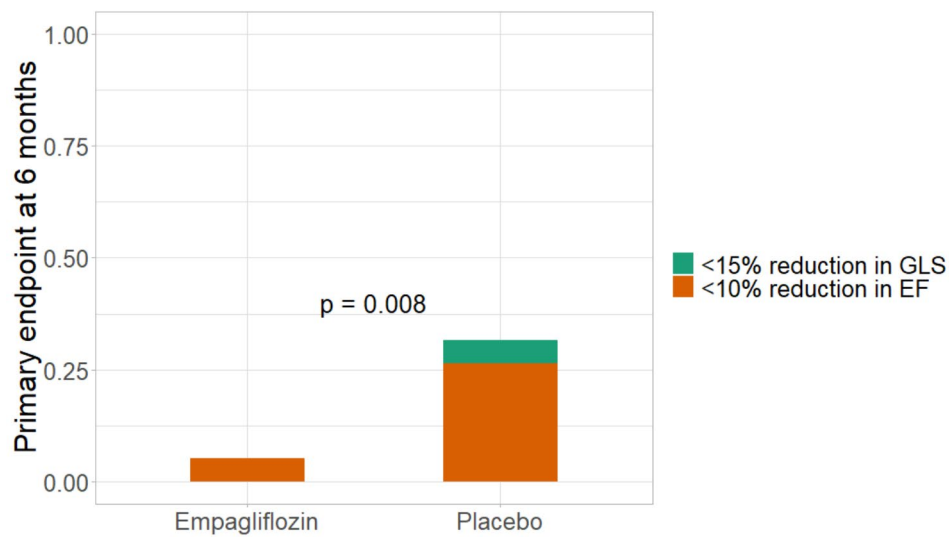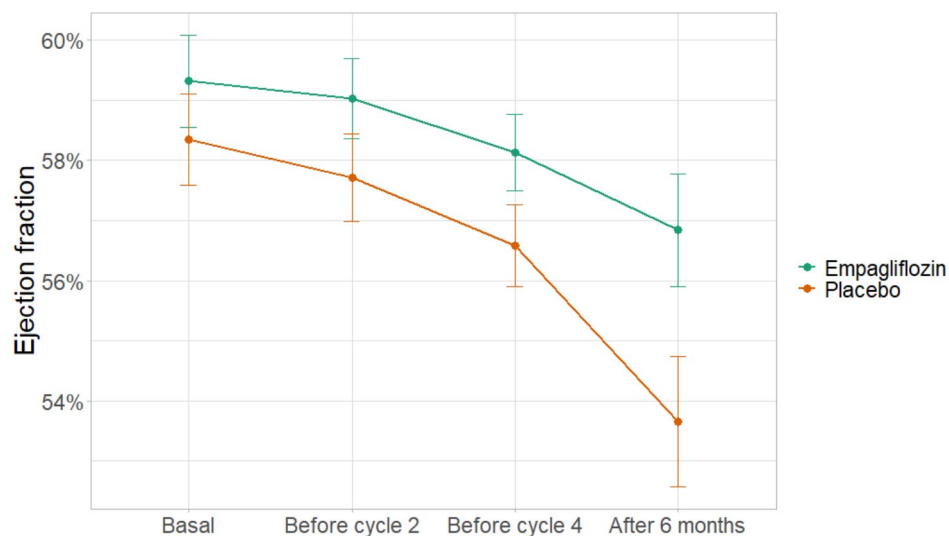
Fig. 2 Primary endpoint results

Fig. 3 Left ventricle ejection fraction over time

therapies have been associated with the emergence of several cancer-related cardiovascular diseases [15], including asymptomatic left ventricular dysfunction and heart failure.

With the advent of cardio-oncology at the beginning of this century, we focused on understanding the pathophysiology of cardiotoxicities to establish, first, early therapies for them and, above all, preventive measures to avoid them and thus ensure that patients can continue their cancer treatment (Figs 2 and 3).

In recent years, several studies have evaluated the usefulness of different drugs for preventing heart failure in patients with CRCTD [16–20].

Over the years, we have witnessed multiple primary prevention strategies in cardio-oncology, with conflicting results. Cardioprotection started with the use of enalapril to prevent LVEF decline in patients who developed an increase in cardiac troponin during anthracycline treatment [21].

Subsequent trials, including OVERCOME, MANTI-CORE, PRADA, and the study by Guglin et al., evaluated the efficacy of beta-blockers, ACEIs, and angiotensin receptor blocker 2 (ARB2) in preventing left ventricular dysfunction in cancer patients [16, 17, 22, 23]. Research has also explored the cardioprotective use of aldosterone antagonists [18, 19, 24], and various studies have investigated whether statins can prevent the occurrence of cancer therapy-related cardiac dysfunction (CTRCD) [20, 25–28].

Table 2 Outcomes according to treatment arm

Characteristic	Empagliflozin, N = 38[1]	Control N = 38[1]	p-value[2]
Ejection fraction decreased by 10%	2 (5.3%)	10 (26%)	0.012
GLS decreased by 15%	2 (5.3%)	12 (32%)	0.003
NT-proBNP elevation	4 (11%)	9 (24%)	0.13
cTnI elevation	6 (16%)	11 (29%)	0.2
Ejection fraction	56.8 (5.8)	53.7 (6.7)	0.029
Clinical heart failure	1 (2.6%)	6 (16%)	0.11
Decreased GFR	1 (2.6%)	4 (11%)	0.4
NYHA functional class			0.4
I	13 (76%)	9 (53%)	
II	3 (18%)	5 (29%)	
III	1 (5.9%)	3 (18%)	
IV	0 (0%)	0 (0%)	
Death or hospitalization due to heart failure	1 (2.6%)	3 (7.9%)	0.6

[1] Mean (SD); n (%)

[2] Wilcoxon rank sum test; Fisher's exact test

Table 3 Adverse effects

Characteristic	Empagliflozin, N = 38[1]	Control, N = 38[1]	p-value[2]
Ketoacidosis	0 (0%)	2 (5.3%)	0.5
Hypoglycemia	1 (2.6%)	1 (2.6%)	> 0.9
Sepsis	1 (2.6%)	2 (5.3%)	> 0.9
Neutropenic fever	1 (2.6%)	2 (5.3%)	> 0.9
Urinary tract infection	1 (2.6%)	4 (11%)	0.4

[1] n (%)

[2] Fisher's exact test

However, the results from these studies have been mixed, possibly due to flaws in study design, endpoint definitions, and the inclusion of patients with varying levels of cardio-oncological risk, predominantly low risk.

A few years ago, a new family of drugs originally developed for the treatment of diabetes, SGLT2 inhibitors (SGLT2is), was found to be beneficial for treating heart failure. Several prospective randomized, double-blind studies have demonstrated that SGLT2i could reduce mortality or hospitalization due to heart failure and improve renal function [5, 6, 29]. Notably, the EMPEROR-Reduced and EMPEROR-Preserved trials led to the approval of empagliflozin for treating heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) [5, 6].

In cardio-oncology, retrospective studies analysing national health databases (Oh CM et al., Gongora et al. and Abdel-Qadir et al.), which include patients with cancer and diabetes receiving anthracycline therapy, have been published [7, 10, 11]. These studies revealed that patients receiving SGLT2i had lower incidences of heart failure, heart failure hospitalizations, new cardiomyopathies, and arrhythmias [7, 10, 11].

The EMPACARD Prevention PILOT trial is a prospective open-label case−control trial designed to evaluate the usefulness of empagliflozin in preventing CTRCD.

At the 6-month follow-up, patients treated with empagliflozin exhibited a smaller decline in global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF). The only significant difference between the placebo and treatment groups in terms of basal characteristics was the use of beta-blockers (58% in the Empagliflozin group and 34% in the placebo group, $p = 0.038$). When adjusting for beta-blocker use, the protective effect of empagliflozin remained significant, with an OR for the primary endpoint for the placebo group of 10.29 ± 2.48 ($p = 0.0055$).

However, there was no statistically significant difference in the secondary endpoints. This absence of a significant difference is likely attributable to the small sample size.

Similarly, exploratory endpoints were not significantly different between the two groups. In terms of safety outcomes, there were no significant differences in the incidence of ketoacidosis, hypoglycemia, sepsis, neutropenic fever, or urinary tract infections between the groups.

The EMPACARD Prevention PILOT trial represents a promising start in investigating the role of empagliflozin as a cardioprotective strategy in patients treated with anthracyclines.

Limitations
The EMPACARD Prevention PILOT series is limited by its small sample size and relatively short follow-up period.

Future directions
Moving forward, it is imperative to conduct a prospective randomized, multicentre study to validate the findings elucidated in our trial. This approach will allow for

a more comprehensive evaluation of empagliflozin's efficacy and safety in reducing anthracycline-induced cardiotoxicity across a broader and more diverse patient population.

Conclusion

In this prospective case-control trial, empagliflozin administered to a high-risk group were associated with a reduction in anthracycline-induced cardiac dysfunction. Furthermore, SGLT2 inhibitors have been proven safe for patients undergoing chemotherapy. These promising findings underscore the need for a clinical trial to explore whether SGLT2 inhibitors can effectively reduce the incidence of heart failure among high-risk patients receiving anthracycline treatment.

Abbreviations

AIC	Anthracycline-induced cardiotoxicity
HF	Heart failure
SGLT2i	Sodium–glucose transport protein 2 inhibitors
HFA/ICOS	Heart failure association/international cardiOncology society
CTRCD	Cancer therapeutic-related cardiac dysfunction
LVEF	Left ventricular ejection fraction
GLS	Global longitudinal strain
HfpEF	Heart failure preserved ejection fraction
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
CV	Cardiovascular

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40959-024-00260-y.

Supplementary Material 1

Declarations

Competing interests
The authors declare no competing interests.

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