Tyrosine Kinase Inhibitor Induced Proteinuria – A Review

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ABSTRACT

Tyrosine Kinase inhibitor (TKI) is a class of drugs that interfere with protein kinases' signal transduction pathways through an array of inhibitory mechanisms. Tyrosine kinases (TK) have an inevitable role in downstream signal transduction and the proliferation of tumour cells. Hence, tyrosine kinase inhibitors (TKIs) are frequently employed as anti-neoplastic agents in the treatment of colon, breast, kidney, and lung cancers. They can be used as single or combination therapy with other targeted therapies. It is understood that TKIs pose a risk of developing proteinuria in some patients as it can primarily result in dysfunction of the split diaphragm, constriction or blockage of capillary lumens mediated by the basement membrane, acute interstitial nephritis, or acute tubular necrosis. This paper reviews the mechanism of action of TKIs, the pathophysiological mechanism of TKI-induced proteinuria, and its management ▶ **Fig. 1**.

Introduction

From routine cytotoxic chemotherapy, cancer treatment has undergone an evolutionary transition to molecular targeted therapy because of advancements in the understanding of pathogenetic mechanisms involved in the biological characteristics of tumours. The typical progression of many cancers, which were once considered incurable, has been drastically altered by these targeted treatments. One such target which revolutionised cancer therapy is Tyrosine Kinase (TK). TK belong to the protein kinase family, which can either be a receptor tyrosine kinase (RTK) or non-receptor tyrosine kinase (NRT) (cytoplasmic tyrosine kinase). Serine or threonine kinases are examples of protein kinase family. These agents also have potential anti-neoplastic activity. These agents mainly target protein kinase B (PKB or AKT) and ribosomal protein S6 Kinase (p70S6K). Numerous malignancies frequently have elevated levels of these kinases. This molecule will cause apoptosis when it inhibits PKB, but it will also impede translation within tumour cells by inhibiting p70S6K. RTK is a transmembrane receptor which is the most common among the 90 identified TK [1]. Common RTKs include vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptor (PDGFR), receptors belonging to the insulin family and ErbB family (EGRF- epidermal growth factor receptors and HER2- human epidermal growth factor receptor-2). NRTK, alternatively referred to as cytoplasmic proteins, encompass nine families: Src, Ack, Syk/Zap70, Fak, Fes/Fer, Csk, Tec, Abl, and Jak. Additionally, there are Rak/Frk, Srm, Rlk/Txk, and Brl/Sik, which are categorized separately from these nine families. Other than these two, dual-specificity kinases (DSK) are also described, of which the most common is MEK (mitogen-activated protein kinase), in the MAP pathways [2–4]. RTK binds to the ligand and undergoes dimerization, which is followed by phosphorylation of tyrosine residue. The phosphorylation causes alteration in genetic transcription, resulting in changes in cell growth and differentiation, enzyme activity as well as cell metabolism and death. It is known that a variety of cancers show upregulated activity of TKs, which can be a potential target for antineoplastic agents, and the in-

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troduction of TKIs in cancer therapy has revolutionized the treatment landscape. TKIs focus on the pathways of signalling associated with intracellular kinases or receptor tyrosine kinases that control cellular growth. Currently, a minimum of 50 TKIs are available for treating various cancers, that have been approved by the FDA [5]. TKIs are classified into 5 Types according to their binding mechanisms. Type 1 inhibitors are those that bind to the ATP-binding site of TKs, Type 2 inhibitors are those that bind to inactive kinases, Type 3 inhibitors are those that only act on the allosteric site of the ATP-binding site, Type 4 inhibitors are those that bind to the allosteric site that is far from the ATP-binding site, and Type 5 inhibitors are those that inhibit kinases by multiple binding mechanisms [6, 7]. The majority of TKIs inhibit numerous kinases, which increases the probability of toxicities that may further lead to an increasing rate of discontinuation. Both excess inhibition of the expected TK function as seen during on-target effects or concurrent inhibition of several other kinases due to limited selectivity as seen due to off-target effects can result in toxicity. Most of the TKIs are administered orally, and the dose needs to be adjusted according to the patient's co-morbidities, tolerance and adverse drug reactions (ADR) [5, 8, 9]. The development of ADR depends on the dose and the profile of the drug [9]. Proteinuria is a relatively common side effect associated with TKIs which is being reported clinically [10–12]. Other than proteinuria, specific hematologic, musculoskeletal, respiratory, and neurological adverse reactions are also seen [13]. Many studies have reported the proteinuria associated with various chemotherapeutics agents, but the studies indicating proteinuria associated with TKI are limited. However, these conditions are common in clinics. In this review, we gain a deeper understanding of the mechanism of action of TKI, the pathophysiology of TKI-induced proteinuria, and its management.

Mechansim of action of TKI

The basis of TKIs lies in disrupting specific upregulated pathways in malignant cells. TKIs inhibit the formation of the autocrine loop (regulated by VEGF, epidermal and platelet-derived growth factor), a regulatory process vital for metastasis and tumour progression. TKIs that inhibit Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR) are pivotal for the management of cancers of the liver and kidney [10]. TKIs competitively inhibit ATP binding to receptor tyrosine kinase (RTK). TKIs also act by effectively blocking the growth factors that the RTK has activated. RTKs become dimerized upon binding with a ligand and use ATP to catalyze the phosphorylation of residues of protein tyrosine, changing the functions of cytoplasmic proteins. Their effect at the genetic level causes changes in cell growth and differentiation, adhesion, metabolism, cell activity, and death [14]. Different TKIs act on separate receptors for inhibition of cell proliferation. The mechanism of action of each TKI molecule and the use of TKI are described in ▶ **Table 1** and ▶ **Table 2**, given below.

TKIs with their common indications are listed in ▶ **Table 2** given below.

Adverse Effects

TKI-associated adverse events can either interfere with the treatment, affect the quality of life (QOL) of the patient, or even lead to the complete termination of therapy. The toxicity associated with TKI can occur due to on-target and off-target effects. On-target effects are because of the excessive inhibition of targeted TK function, and the off-target effect is due to the concurrent inhibition of several other kinases, which have low selectivity. Most seen adverse events (AEs) during VEGF pathway inhibition by TKIs include hypertension, wound healing complications, cardiovascular and haematological toxicities, and renal toxicity, among others. Although the toxicity associated with TKI is rarely life-threatening, the patient's QOL may be adversely affected [14].

Among the possible adverse events mentioned above, renal impairment involving proteinuria certainly gains attraction due to its occurrence rate (21–41 % in patients who received low dose TKI), its effect on the patient's QOL, and the lack of efficient management principles for the same. Although the mechanism behind proteinuria is unclear, the available data suggests that thrombotic microangiopathy leading to inhibition of podocytes, focal segmental glomerulosclerosis, and glomerulopathies. Studies on anti-VEGF renal adverse events suggest that proteinuria accounts for 21 % to 63 % of all renal side effects. Meta-analyses involving VEGFR-targeted TKIs showed incidences of 2.4 % for high-grade proteinuria and 18.7 % for other lower grades. Results of phase II clinical trials on TKIs showed an incidence of 58 % and 83 % of proteinuria associated with Regorafenib and Lenvatinib, respectively [17, 18]. Among patients on Lenvatinib therapy, proteinuria was the common ADR, and 52 % experienced a reduction in dose during treatment. The same was the case when ramucirumab (VEGFR2 monoclonal antibody) was combined with erlotinib (an EGFR inhibitor), where proteinuria was significantly higher when compared with ramucirumab monotherapy (ramucirumab vs. ramucirumab + erlotinib: 20 % vs. 34 %) [20].

The toxicities of the TKI mainly depend on the inhibited targets (single or multikinase inhibitors), the strength of target inhibition (affinity to the tyrosine kinase, 'on- and off-target' toxicities), and the type of inhibited target (PDGF inhibition versus Flt-3 inhibition, VEGF inhibition versus platelet-derived growth factor). Some of the toxicities are associated with the target site, which includes hypertension [21]. Inhibition of VEGF can lead to reduced generation of nitric oxide (NO) from the endothelial cells, which leads to dysregulated vasoconstriction causing hypertension [22]. Fatigue, asthenia are other adverse effects related with inhibition of VEGF [23]. Hypothyroidism may be caused by several VEGF inhibitors [24]. Hypophosphatemia has also been described with VEGF inhibitors. VEGF inhibition can lead to the inhibition of AKT and mTOR, which can lead to muscle loss [25].

Another on-target adverse effect related to TKI is proteinuria [26]. Cardiac toxicities can occur because of on-target and off-target-based inhibition [27, 28]. Hand-foot syndrome is reported to occur between 14 to 28 days of VEGF inhibition. Myelotoxicity can occur because of on and off-target toxicities [29]. Tyrosine kinase inhibitors, for example, sunitinib inhibit the KIT signalling pathway. Common toxicities seen during sunitinib treatment include nausea, fatigue, hand-foot syndrome, anaemia and renal adverse events. Inhibiting VEGF can also lead to myelotoxicity [30, 31]. TKI inhibits vasoactive substances like PG and NO, which are crucial for mucosal defence and GI cell turnover [32].

▶ **Table 1** Mechanism of action of some commonly used TKIs [10, 14].

Drug	Mechanism of Action
Sunitinib	Blocks VEGFRs,c-Kit and 1–3, platelet-derived growth factor receptor-α (PDGFR-α), and PDGFR-β, FLT3, CSF1R, and RET
Vandetanib	Inhibits EGFR, VEGFR2–3, and RET
Sorafenib	Receptor antagonist to many protein kinases and inhibits PDGFR-β, and RAF-kinases along with VEGFR-2 and VEGFR-3, KIT, and BRAF
Crizotinib	Inhibits ALK and c-MET receptors
Pazopanib	Blocks IL-2-inducible T-cell kinase, macrophage colony-stimulating factor 1 receptor (c-Fms), fibroblast growth factor receptors-1 (FGFRs-1), FGFRs3 and lymphocyte-specific protein tyrosine kinase, VEGFR1–3, c-Kit, PDGFR-α and PDGFR-β
Lapatinib	Targets EGFR, preferentially HER2
Regorafenib	Blocks TIE2, RET, VEGFRs, and KIT
Gefitinib	Targets EGFR
Erlotinib	Targets bEGFR, preferentially HER1
Afatinib	Targets EGFR, preferentially HER1
Axitinib	Blocks c-Kit, VEGFR1–3 and PDGFR
Cediranib	Inhibits PDGFR, KIT and VEGFRs

▶ **Table 2** TKIs with their common indications.

Drug	Indications	References
Imatinib	Gastrointestinal stromal tumors Low-risk chronic myeloid leukemia	[15]
Sunitinib	Gastrointestinal stromal tumors (GIST) Pancreatic NET Renal cell carcinoma	[16]
Regorafenib	Gastrointestinal stromal tumors (GIST) Colorectal cancer Hepatocellular carcinoma	[17]
Sorafenib	Thyroid cancer Hepatocellular carcinoma Renal cell carcinoma	[16]
Lenvatinib	Thyroid cancer Hepatocellular carcinoma	[18]
Cabozantinib	Metastatic medullar thyroid carcinoma	[17]
Vandetanib	Metastatic medullar thyroid carcinoma	[17]
Lapatinib	Breast cancer	[19]
Erlotinib	NSCLC Pancreatic cancer	[15]
Gefitinib	NSCLC	[15]
Dasatinib	CML	[15]
Nilotinib	CML	[15]

Pathophysiology of TKI-induced proteinuria

Proteinuria, the loss of protein in the urine, is a dose-related side effect that appears after inhibiting VEGF signalling and further causes glomerular damage [26]. According to a study by Baek et al., proteinuria was associated with sunitinib in 17.6 % of patients and worsened in 23.1 % of patients. A study by Miyake et al.shows that proteinuria affected 41.5 % of the patients given axitinib [33]. A case report by Shiva et al. showed that sorafenib can induce nephrotic syndrome in post-transplant HCC patients. The measurement of proteinuria was based on 24-hour urine levels, a urine dipstick test, or a urine protein-creatinine ratio. A value of 1 + on the dipstick or 0.15–1.0 g/24 h urine protein level was considered grade 1. Grade 2 included 2–3 + on dipstick or > 1.0–3.5 g/24 h protein, whereas a value of 4 + on dipstick or > 3.5 g/24 h was considered grade 3 proteinuria [10]. A clinical trial on sorafenib has reported that proteinuria has occurred in 21–36 % of patient. Also, studies have reported that the incidence of proteinuria was in patients who are on regorafenib and lapatinib with a rate of 58 % and 83 %, respectively. A case report from Japan has reported that Dasatinib, a kinase inhibitor which acts on the ABL kinase domain, is associated with nephrotic syndrome in a CML patient [34]. Also, a study by Ali et al. in the year 2017 reported that Dasatinib can cause proteinuria, which can be reversed with treatment. Another case report on sorafenib-induced nephrotic syndrome has been reported in recurring post-transplant HCC patients [35].

The exact pathophysiology of proteinuria associated with TKI is still unknown. Proteinuria due to anti-VEGF therapy can mainly be brought on by split diaphragm dysfunction, basement membrane-mediated capillary luminal narrowing or occlusion, acute interstitial nephritis, or acute tubular necrosis. The vascular damage referred to as thrombotic microangiopathy is one of the most typical pathological changes. Other pathological changes involve focal segmental glomerulosclerosis lesions (FSGS), acute interstitial nephritis, crescent-shaped glomerulonephritis, immune complex-mediated glomerulonephritis, and minimal change nephropathy (MCN). Tubular necrosis and acute tubular injury represent two more possible pathological changes in TKI-induced proteinuria, which were seen in some biopsies [10].

The VEGF formed by the podocytes crosses the GFB (glomerular filtration barrier) and reaches the surface of the endothelium, where it interacts with Flk1 (VEGF receptor 1) and Flt1 (VEGF receptor 2) receptors [36]. The vascular permeability of the glomerulus is sustained with the interaction of VEGF, which is generated on glomerular endothelial cells from VEGFR-2 and podocytes. When VGEF gets inhibited, it inhibits nephrin, which is a protein that is crucial for preserving the glomerular split diaphragm and can interrupt the GFB. VEGF inhibition can lead to deprivation of endothelial fenestration in the capillaries, proliferation of glomerular endothelial cells and podocyte depletion. Reduced expression of nephrin following VEGF inhibition leads to injury of the podocyte, resulting in proteinuria. There is depletion of endothelial fenestrations in the glomeruli, swelling endothelial cell cytoplasm as well as destruction of podocyte. Also, some studies have evidence that the damage of podocytes can occur through c-mip, a protein that can interact with the nephrin or AKT signalling pathway [36]. This protein decreases the phosphorylation of nephrin, which can lead to cytoskeletal disorganisation and can cause dysfunction to slit diaphragm. This c-mip gets abundantly increased with anti-VEGF treatment and can develop into MCN and FSGS. When TKI attaches to the c-mip promoter, it leads to reduced RelA expression and subsequent repression of transcription. The increased RelA level is expressed in thrombotic microangiopathy. A study by Echeverria et al. shows that sorafenib can inhibit NF-κB, which further

leads to overexpression of c-mip and indirectly leads to podocyte disease with proteinuria [37].

Sunitinib in hepatocellular carcinoma, small-cell lung cancer, and ovarian carcinoma showed widening of the subendothelial area of glomerular capillaries along with thrombotic microangiopathy, modest mesangial deposition of IgA, and duplication of the glomerular basement membranes with cellular interposition. Acute interstitial nephritis with polynuclear infiltration was found in metastatic renal cell cancer patients on sorafenib [10, 26].

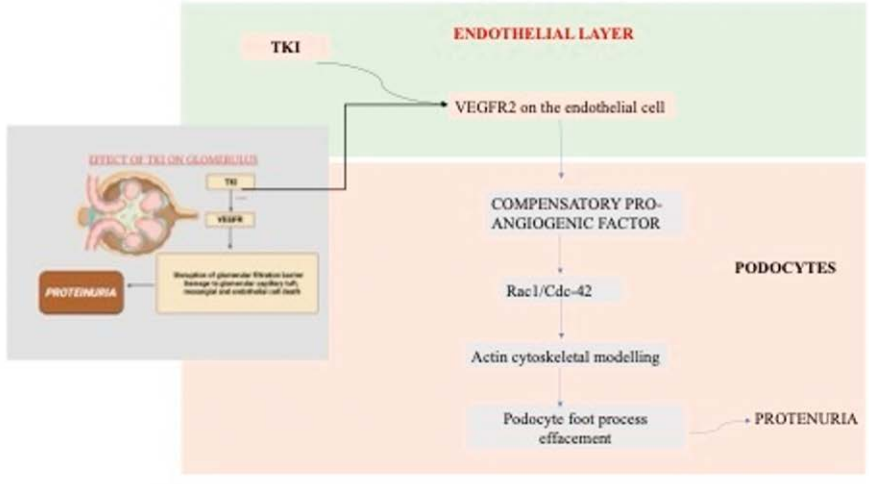
Research led by Yunfeng Ruan et al. in the year 2016 on Chinese lung cancer patients has reported that adverse effect associated with TKI is associated with certain genetic factors. The SNP in the EGFR pathway can vary interpersonally and this variation may be influenced by drug metabolism/transport pathways and miRNA, but further research is needed to completely understand biomarkers for therapeutic responses and ADRs to TKIs in the Chinese demographics. Proteinuria associated podocyte damage caused by TKI can change the RelA signaling pathway [38]. ABCG2 polymorphism is found to have sunitinib-induced toxicity in metastatic renal cell carcinoma patients. ABC transporters also play a role in the pharmacokinetics of erlotinib, sunitinib and sorafenib [39]. The role of SNP in TKI-induced proteinuria is not well established. However, the drug metabolizers, as well as transporters, may lead to toxicity. Further studies are warranted to confirm the role of SNP variation-associated proteinuria.

Management of TKI Induced Protenuria

Proteinuria is associated with cardiovascular abnormalities and contributes to the development of kidney diseases. With the improvement in survival of various cancers due to newer therapies, it is necessary to find appropriate methods for the management of various adverse events. Evidence-based management of proteinuria associated with TKI is lacking. Currently, to overcome this side effect of TKI, treatment is initiated after screening for proteinuria and hypertension. To portray the renal indications of proteinuria more accurately with TKI and to rule out underlying conditions like TMA, certain patients with high-grade proteinuria may warrant a renal biopsy with a reduced threshold [3, 26, 40].

Certain recurrent and advanced cancers warrant the use of TKIs, and most of these patients may later develop proteinuria and hypertension. Angiotensin-converting enzyme inhibitors (ACEI), which form the first line of management of hypertension, can be considered here as well. It has been reported that the use of ACEI for the management of proteinuria is effective. The initiation of ACEI requires close monitoring of the creatine and potassium levels. Angiotensin receptor blockers may also be used for proteinuria, as there is less evidence suggesting a rise in angiotensin and renin associated with TKI use. Unexplained proteinuria warrants renal biopsy and further management. In scenarios where alternative therapies are limited, we need to evaluate the risks and benefits of using TKI [41, 42]. It is necessary to titrate the dose of ARB or ACEI for maximum anti-proteinuric action. The ROAD trial has reported the benefits of titration of an ARB or an ACEI toward proteinuria and its renal outcome [43]. As of now, there has been no discernible difference between the efficaciousness and adverse-effect profiles of ARBs and ACE inhibitors. As a result, the provider's experience and the patient's response should confirm the choice. Other agents like diuretics and calcium channel blockers are recommended for the management of TKI-induced proteinuria. Diuretics include aldosterone antagonists like spironolactone, whereas calcium channel blockers include diltiazem and verapamil [44, 45]. However, the evidence for the efficacy of these 2 agents against TKI is limited. Studies are warranted for its routine use in clinics. The detailed dose of ACEI or ARB is mentioned in ▶ **Table 3**, given below. The general management of proteinuria is depicted in the ▶ **Fig. 2** given below.

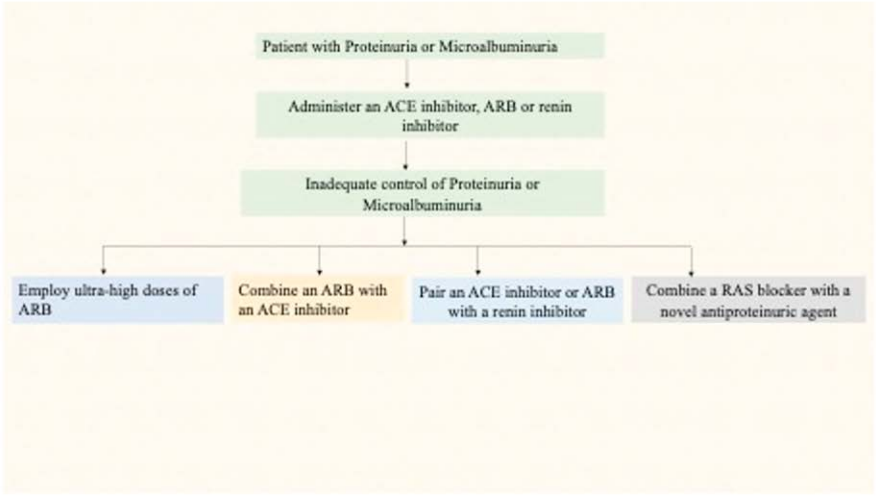
The detailed dose of ACEI or ARB is mentioned in the ▶ **Table 3** given below.



▶ **Fig. 1** Graphical Representation of TKI induced protenuria.

▶ **Table 3** The detailed dose of ACEI or ARB for management of TKI induced protenuria.

Co-morbidities	Drugs for proteinuria management	Doses	References
Type 1 Diabetes	Lisinopril	40 mg	[46]
Patient with renal insufficiency and are non-diabetic	Benazepril	> or = 20 mg	[43]
≥ 1 g of proteinuria	Candesartan	128 mg/day	[47]
Patient having type 2 DM and protenuria	Irbesartan	900 mg/day	[48]
Type 2 diabetic with hypertension and UAER 20–700 µg/min	valsartan	320–640 mg/day	[49]
Patient having proteinuria and are non-diabetic	Telmisartan	80 mg b.i.d.	[50]
Nephropathy due to type 1 Diabetes	Losartan	100 mg/day	[51]
Patient who is non-diabetic having proteinuria and renal impairment	Losartan	> or = 100 mg	[43]



▶ **Fig. 2** Schematic representation of management of TKI induced protenuria.

The paradigm shift to precision oncology warrants an increase in the usage and role of TKIs in current-day oncology practice. Apart from that, as oncology clinics have a substantial waiting list for chemotherapy, patients frequently have to wait weeks to begin intravenous treatment. In addition, a large number of patients are elderly and unable to visit the clinic on their own for intravenous treatment. In addition to taking time off work to transport patients for treatment, other family members frequently take on the role of caregiver. For this reason, giving TKI orally is much more convenient than intravenous chemotherapy [44]. Lastly, chemotherapy is frequently intolerable for specific individuals, such as those with comorbidities or poor performance status. For those patients, less intrusive therapies like TKIs are therefore preferred [52].

Conclusion

TKI-induced proteinuria is a significant and it is the most recognized adverse effect in patients undergoing treatment with tyrosine kinase inhibitors. While the precise mechanisms remain under investigation, the management of proteinuria is critical to ensuring patient safety and optimizing therapeutic outcomes. Despite the high tolerance rate, their utilization is limited due to notable toxicities that compromise the patient's quality of life. Such adverse effects connected to pathway inhibition may disrupt treatment or cause it to be stopped altogether. TKI-related proteinuria is common, and its severity and quick onset can be worrisome, but studies associated with TKI induced proteinuria is less . It also has adverse cardiovascular outcomes. Although the first line of treatment for proteinuria involves angiotensin-converting enzyme inhibitors, treating or removing the drug from therapy is a more efficient approach to managing this situation. It is crucial to recognize such side effects in order to improve cancer treatment outcomes and survival. Effective management of TKI-induced proteinuria includes proper selection of candidates for treatment, making decisions regarding interruption of treatment, adjustment of dosage, and cessation of therapy. Physicians should also be open to considering alternatives to VEGF-targeted therapy for patients at greater risk of intolerable anti-VEGF-related toxic effects. The proteinuria associated with TKI might be due to alteration in the transport or metabolism of the drug, which occurs due to the SNP variation in an individual. As long as pharmacogenetic studies are lacking, therapeutic drug monitoring can be used to assess the drug concentration in an individual and can correlate with toxicities. Further studies are warranted

in pharmacogenetic and pharmacokinetic aspects to rule out the exact reason for TKI-induced proteinuria.

Author's contribution

All author's contributed equally to this work.

Conflict of Interest

Authors declare no conflict of interest associate with this publication.

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