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OPINION PAPER

Revisiting treatment of pulmonary arterial hypertension in the current era: a Greek scientific document

Eftychia Demerouti,[1] Frantzeska Frantzeskaki,[2] Tonia Adamidi,[3] Anastasia Anthi,[4] Effrosyni Filiou,[3] Panagiotis Karyofyllis,[1] Athanasios Manginas,[5] Ioanna Mitrouska,[6] Stylianos E. Orfanos,[7] Georgia Pitsiou,[8] Iraklis Tsangaris,[2] George Giannakoulas[9]

ABSTRACT

Pulmonary arterial hypertension (PAH) is a life-threatening condition characterised by the excessive proliferation of pulmonary artery vessels. Despite significant advancements in treatment strategies over recent years, mortality rates remain high. The current treatment strategy focuses on risk assessment both at the time of diagnosis and during follow-up. It involves the initial use of combination therapies targeting PAH. These therapies regulate vascular tone through 3 main pathways: the endothelin pathway, the nitric oxide/cyclic guanosine monophosphate pathway, and the prostacyclin pathway. Sotatercept, a fusion protein that binds to ligands of the transforming growth factor-β superfamily, rebalances the pro- and anti-proliferative signalling of activin receptor type II (A/B), thus targeting a unique pathogenic pathway and promoting anti-proliferative effects on the pulmonary vasculature. Recently, it received approval from the European Medicines Agency for patients with PAH classified as World Health Organisation functional class II or III. Proceedings from the latest World Symposium on Pulmonary Hypertension stress the importance of adding sotatercept to the treatment regimen for the majority of patients during follow-up, including those at high risk. In anticipation of upcoming scientific guidelines and with the hope of improved outcomes for patients with PAH, an expert opinion for the treatment of Greek patients has been developed, focusing on the integration of this novel agent into the therapeutic algorithm.
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1. INTRODUCTION—CURRENT DATA ON PULMONARY ARTERIAL HYPERTENSION TREATMENT

Pulmonary arterial hypertension (PAH) is a severe, incurable disease characterised by pulmonary vascular remodelling, leading progressively to elevated pulmonary vascular resistance and pulmonary artery pressure, which ultimately affects right ventricular function.[1] This remodelling is a complex, dynamic process driven by an imbalance of vasoconstrictive and vasodilating agents from the pulmonary

[1]Department of Cardiology, Onassis Cardiac Surgery Centre, Athens, Greece
[2]2nd Department of Critical Care, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[3]Respiratory Department, Nicosia General Hospital, Cyprus
[4]1st Department of Critical Care National and Kapodistrian University of Athens Medical School, and Pulmonary Hypertension Clinic, Evaggelismos General Hospital Athens, Greece
[5]Department of Cardiology, Mediterraneo Hospital, Athens, Greece
[6]Department of Thoracic Medicine, University Hospital of Heraklion, Heraklion Crete, Greece
[7]National & Kapodistrian University of Athens, Medical School, Athens, Greece
[8]Respiratory Failure Clinic, Aristotle University of Thessaloniki, "G. Papanikolaou" Hospital, Exohi, Thessaloniki, Greece
[9]Department of Cardiology, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
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ABBREVIATIONS

PAH = pulmonary arterial hypertension

HOPE = hellenic pulmonary hypertension registry

ERAs = endothelin receptor antagonist

PDE5i = phosphodiesterase-5 inhibitor

sGCs = soluble guanylyl cyclase stimulator

TGFβ = transforming growth factor-β

BMP = bone morphogenetic protein

ActARIIa = activin receptor type II A

PVR = pulmonary vascular resistance

6 MWD = 6-Min walk distance

mPAP = mean pulmonary arterial pressure

RV = right ventricular

HPAH = hereditary PAH

PH = pulmonary hypertension

SVI = stroke volume index

SvO2 = mixed venous oxygen saturation

endothelium, altered regulation of vascular smooth muscle cells and fibroblast proliferation, an abundance of inflammatory mediators, and involvement of intricate signalling pathways.[2]

Before targeted therapies became available, the prognosis for PAH was bleak. The introduction of epoprostenol in the late 1990s marked a revolutionary improvement in survival rate for patients with PAH.[3] Over the past 3 decades, additional targeted treatments have improved haemodynamic parameters, exercise tolerance and time to clinical worsening.[4,5] However, most randomised studies of current therapies, except intravenous epoprostenol, have not demonstrated significant reductions in mortality, though meta-analyses and observational studies suggest a modest decrease in all-cause mortality.[6] Median survival remains less than 10 years from diagnosis,[5] with 3- and 5-year survival rates unchanged over the past 2 decades, according to national and international registries.[7] In Greece, the Hellenic Pulmonary Hypertension Registry (HOPE),[8,9] launched in January 2015, has enrolled 544 patients with PAH as of January 2025. Of these, 37.1% have idiopathic/hereditary PAH, 38.2% connective tissue disease-associated PAH, 18.6% congenital heart disease-associated PAH, 1.1% drug-induced PAH, 0.4% human immunodeficiency virus infection associated -PAH, 2.9% portopulmonary hypertension and 1.7% pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis. The majority of patients receive combination drug therapy for PAH. Overall, 1-, 3- and 5-year survival rates were 89%, 74% and 67%, respectively, comparable to other national registries.[10] Across all registries, a lack of improvement in survival remains a key finding, despite adherence to recommended treatment strategies.

Current PAH treatments target the 3 main pathways involved in disease pathophysiology: endothelin receptor antagonists (ERA: ambrisentan, bosentan, macitentan), phosphodiesterase-5 inhibitors (PDE5i: tadalafil, sildenafil)/soluble guanylate cyclase activators (sGCs: riociguat), and prostacyclin analogues (epoprostenol, treprostinil)/prostacyclin receptor agonists (selexipag). Even when already on prostanoid by modulating pulmonary vascular tone, leading to vasodilation and improvements in haemodynamics and exercise capacity; however, their effect on patient survival and the disease progression remains unproven.[11] Enhancing the application of existing therapies, particularly parenteral prostanoids, and exploring new therapeutic targets are therefore essential.

Ongoing translational and clinical research has deepened our understanding of the multifactorial mechanisms underlying pulmonary vascular remodelling, revealing novel therapeutic opportunities. Recent insights into the role of transforming growth factor-β (TGFβ) superfamily signalling in PAH pathophysiology of the disease have led to a new treatment approach.[1] Sotatercept, a fusion protein targeting TGFβ-related activin ligands, has recently been approved by the United States Food and Drug Administration (March 2024) and the European Medicines Agency (EMA, September 2024) and incorporated into the treatment guidelines from the 7th World Symposium on Pulmonary Hypertension, establishing activin-TGFβ signalling as a fourth therapeutic pathway targeting pulmonary vascular cell proliferation.[12]

This article aimed to re-evaluate PAH treatment strategies in light of recent therapeutic developments and to present a Greek perspective on a practical therapeutic algorithm for this challenging disease. Similar expert opinion manuscripts from various Central and Eastern European countries, as well as the USA, have highlighted the importance of incorporating sotatercept into clinical practice and proposed treatment algorithms for patients with PAH.[13–15]

2. THE NEW ERA OF PAH TREATMENT

Recent research has highlighted the importance of bone morphogenetic protein (BMP) and TGFβ signalling pathways in the pathobiology of pulmonary vascular remodelling.[12] In heritable PAH (HPAH), the most commonly implicated gene is *BMPR2*, which encodes the BMP receptor type II of the TGFβ superfamily. Other TGFβ superfamily members, including activin receptor type II A (ActARIIa) and its ligands, activin A and activin B, are also involved.[16] The BMP and activin pathways consist of 2 main branches: the TGFβ-activin-nodal signalling through SMAD2/3 and the BMP-GDF branch signalling through SMAD1/2/3[2]. In PAH, impaired BMP/SMAD 1/2/3 signalling, along with overactive activin/SMAD 2/3 responses, contributes to PAH pathobiology, through various mechanisms, such as enhanced smooth muscle cell proliferation, pulmonary endothelial cell apoptosis, inflammatory cell recruitment, vasoconstriction and disrupted homeostasis, promoting vascular remodelling, even in non-HPAH types.[17]

Research into TGFβ pathway-targeted therapies is ongoing to restore the balance between proliferative activin signalling and anti-proliferative BMP

signalling. Sotatercept, an effective ligand trap for activin, represents the first agent targeting this fourth PAH therapeutic pathway within the activin-TGFβ superfamily. Sotatercept's mode of action differs from traditional PAH therapies, focusing instead on rebalancing proliferative and anti-proliferative signals in the pulmonary vasculature.[17]

In the phase 2 PULSAR study sotatercept significantly reduced pulmonary vascular resistance (PVR) and improved 6-min walk distance (6MWD) in patients with PAH after 24 weeks of treatment compared with placebo. Among the 106 adults enrolled, 56% were on triple therapy, and 37% were receiving parenteral prostanoids.[18] The phase 3 STELLAR study further demonstrated the sotatercept's benefits in patients with PAH in the World Health Organisation Functional Class (WHO-FC) II or III on background therapy.[19] Sotatercept increased 6MWD by 40.8 m (95% CI: 27.5-54.1, $p < 0.001$) and improved 8 of 9 secondary endpoints, including NT-proBNP levels, PVR, the PAH-SYMPACT patient-reported outcome, and time to clinical worsening or death, with an 84% relative risk reduction compared with placebo. Echocardiographic findings indicated improved right heart function, with increased tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio, reduced end-systolic and end-diastolic right ventricular (RV) areas, decreased tricuspid regurgitation, and improved RV fractional area change. Adverse events included elevated haemoglobin (6%), thrombocytopenia (6%), telangiectasia (10%), and bleeding complications (20%). Haemodynamic analysis of STELLAR suggested that sotatercept's mechanism may include pulmonary vascular reverse remodelling, as reductions in mean pulmonary arterial pressure were seen without significant changes in cardiac output.[20]

Based on these promising results, sotatercept appears to be a well-tolerated, effective new agent for PAH, acting via the newly recognised activin-TGFβ pathway involved in cell proliferation. Given its beneficial effects on quality of life and disease progression, sotatercept may now be integrated into a modern PAH therapeutic algorithm.

3. TREATMENT ALGORITHM IN PAH. A GREEK PERSPECTIVE IN THE ERA OF SOTATERCEPT

3.1. THE TREATMENT ALGORITHM JOURNEY. In 2003, the 3rd World Symposium on Pulmonary Hypertension introduced the first evidence-based treatment algorithm with levels of evidence to guide clinicians on optimal treatment options for patients with PAH.[21] In 2008, the 4th World Symposium presented an updated algorithm that incorporated the latest evidence, introducing sequential combination therapies for the first time.[22] The algorithm was further refined at the 5th World Symposium in 2013, as advances in clinical and translational research led to a proactive approach towards risk assessment and treatment goals in PAH.[23] The 2015 ESC/ERS Guidelines then recommended a risk assessment tool for use at baseline and during follow-up.[24] This was modified in the 2022 Guidelines, reflecting insights from the 6th World Symposium in 2018, with the introduction of a new non-invasive, 4-strata risk model for improved follow-up stratification.[25] At the 7th World Symposium in 2024 in Barcelona, an updated evidence-based treatment algorithm was presented, along with enhanced risk stratification tools and ambitious treatment goals.[12,26] Experts emphasised that patients with PAH should be reassessed within 3-4 months after the initial diagnosis and treatment initiation and periodically thereafter. Risk assessments should be supplemented with haemodynamics, RV imaging, and other measures when needed. This rapidly evolving landscape in treatment algorithms, combined with the persistently high mortality rate in PAH, underscores the need for alternative management strategies to address this life-threatening disease.

3.2. A SUPPLEMENT RISK ASSESSMENT. According to the 2022 ESC/ERS guidelines,[25] the treatment goal for PAH is achieving a low-risk profile using a tool based on 3 non-invasive parameters: WHO-FC, 6MWD, and BNP/NT-proBNP levels. These parameters are integral to the 4-strata model for risk stratification during follow-up. However, despite their prognostic value, this approach has inherent limitations.[27]

First, these parameters are influenced by other factors such as age, body weight, physical fitness and comorbidities. Second, in younger patients, PAH severity may be underestimated, as they may achieve a better WHO-FC or an overestimated 6MWD. Third, these parameters lack disease specificity. Moreover, the 4-strata tool may not adequately guide therapy in patients with a worse prognosis, such as those with connective tissue disease or HPAH.

Given the severity of PAH, parameters that more directly reflect PH severity and/or RV dysfunction—key predictors of survival—are essential for informed treatment decisions. Haemodynamic and imaging measures can address some limitations of non-invasive parameters, allowing for a more precise treatment approach. Low-risk haemodynamic parameters, per the 3-strata ESC/ERS risk stratification, as well as achievement of normal or near-normal RV

function, assessed through echocardiography or cardiac magnetic resonance imaging, could serve as universal treatment goals.[28] These parameters allow physicians to more accurately stratify low-risk patients during follow-up by verifying the presence of low-risk haemodynamic or RV imaging markers according to the 3-strata model.[29] In other words, for low-risk patients at follow-up, the coexistence of low-risk haemodynamic or echocardiographic parameters enhances the granularity of risk assessment, helping clinicians identify those who may benefit from a more aggressive therapeutic approach.

An intermediate-low or intermediate-high risk status during follow-up is generally suboptimal for most patients with PAH, particularly those without cardiac or lung comorbidities. Some of these patients may require repeat haemodynamic assessment via right heart catheterisation. Notably, Boucly et al. showed that among intermediate-risk patients, stroke volume index (SVI) and mixed venous oxygen saturation (SvO_2) were the best haemodynamic predictors of transplant-free survival.[29] Specifically, having at least one criterion (SVI $>$ 37 mL m^{-2} or $SvO_2 > 65\%$) predicted better outcomes, with 3-year survival rates dropping from 81% to 69% in intermediate-low-risk patients lacking these criteria. Similarly, intermediate-high-risk patients with low-risk haemodynamic parameters demonstrated a 3-year survival rate of 56%, compared with 40% for those lacking these parameters. Consequently, at the first follow-up, intermediate-low-risk patients without low-risk haemodynamic criteria should be reclassified as intermediate-high risk and treated accordingly. Likewise, intermediate-high-risk patients who do not meet these criteria may be reclassified as high-risk and managed with more aggressive treatment strategies.

3.3. PROPOSED TREATMENT ALGORITHM. In Greece, patients with PAH benefit from specialised care nationwide, aligned with international guidelines and offering access to all globally approved treatment options. Given the discrepancies between the 2022 ERS/ESC Guidelines and the 2024 WSPH proceedings regarding treatment approaches, and following the approval of sotatercept in Europe, a multidisciplinary team of cardiologists, pulmonologists, and intensivists managing PAH in Greece has developed a country-specific perspective on an updated treatment algorithm. This patient-focused algorithm integrates sotatercept, a novel activin signalling inhibitor, into the range of available therapeutic options (Fig. 1).

Initial combination therapy forms the foundation of treatment for all PAH patients. For those at low or intermediate risk, the first-line approach involves the combination of an ERA and a PDE5i. In contrast, for high-risk patients, the addition of a parenteral prostanoid is a crucial therapeutic strategy. The first follow-up is recommended within 3-4 months, during which further treatment adjustments are necessary for patients who fail to achieve low-risk haemodynamic or echocardiographic parameters, as defined by the ESC 3-strata risk stratification model.

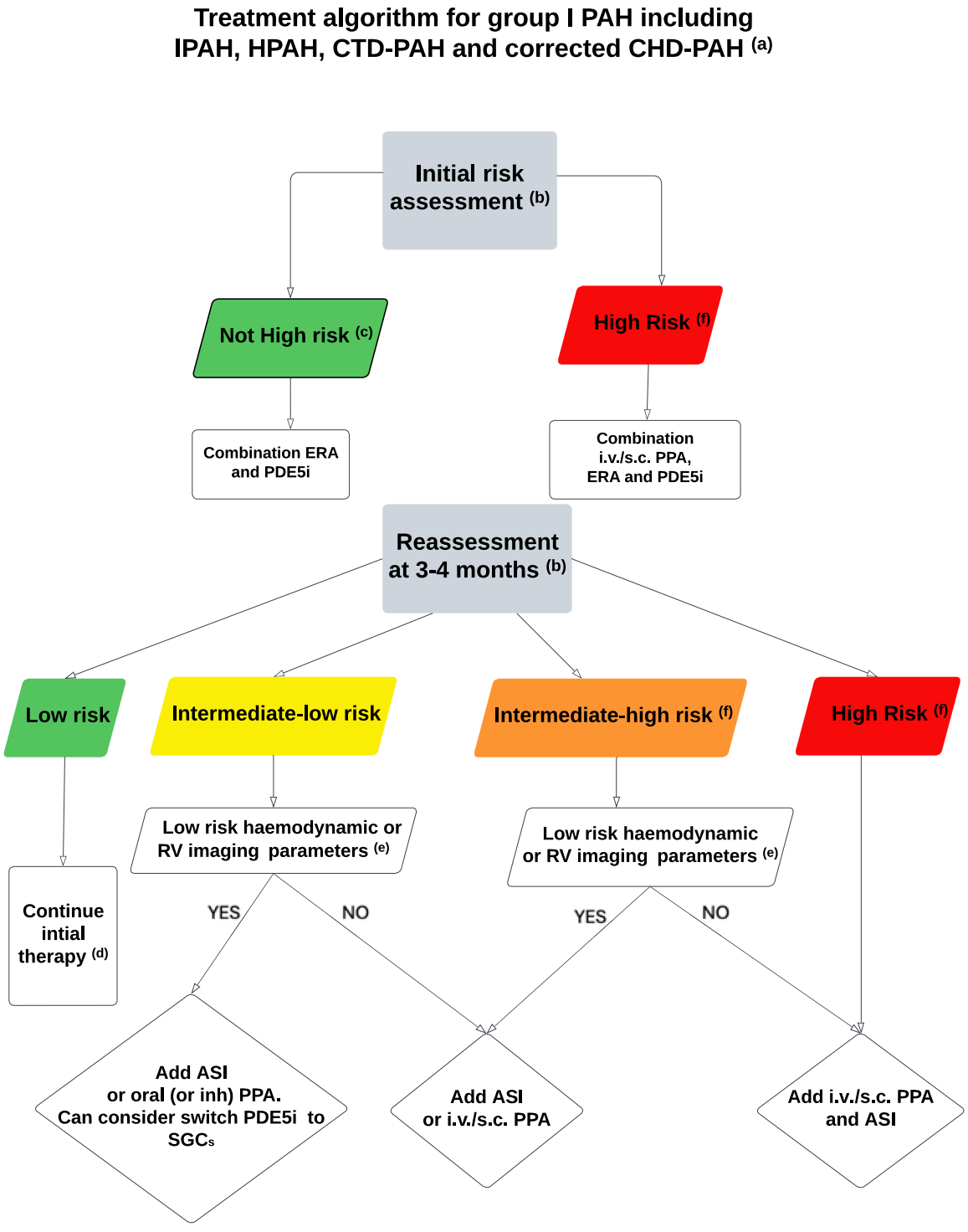
The recently announced phase 3 ZENITH trial (ClinicalTrials.gov identifier NCT04896008), which investigated sotatercept in 172 patients with PAH WHO-FC III-IV at high risk of mortality, was discontinued early due to compelling results. The trial demonstrated a significant and clinically meaningful reduction in morbidity and mortality events in high-risk patients receiving sotatercept compared with placebo.[30] Consequently, high-risk patients identified during follow-up should be managed with a combination of prostanoids and sotatercept to optimise outcomes. Finally, transplant evaluation should be considered for high-risk patients at the time of diagnosis and is recommended for all patients who remain at intermediate-high or high risk during follow-up. Encouragingly, the Greek lung transplantation programme has shown initial promising outcomes, offering hope for successful management in these patients.

3.4. PRACTICAL CONSIDERATIONS ON SOTATERCEPT USE. According to EMA labelling, sotatercept is indicated for adult patients with PAH in WHO-FC II or III to improve exercise capacity. The panel agreed that the majority of patients with PAH in the country (excluding those ineligible, such as patients with Eisenmenger syndrome or those with portopulmonary hypertension) could benefit from treatment with this drug, with therapy outcomes closely monitored. Specialist nurses should be available for patient education and home care support.

Sotatercept is administered subcutaneously every 21 days, starting with an initial dose of 0.3 mg/kg, followed by an increase to 0.7 mg/kg at the second visit. Haemoglobin levels and platelet counts should be monitored for at least the first 5 doses, or longer if values remain unstable. Treatment should be delayed if:

- Haemoglobin level increases by >2 g/dL from the previous value and exceeds the upper limit of normal (ULN),
- Haemoglobin level rises by >4 g/dL from baseline,

FIGURE 1 **Proposed treatment algorithm in PAH**



a. Non-vasoreactive patients (vasoreactive patients should be initially treated with calcium channel blockers). b. Risk assessment is based on ERS/ESC 3-strata model (at baseline) or 4-strata model (during follow-up). c. Initial triple therapy including an i.v./s.c. PPA may be considered in non-high-risk patients with severe haemodynamics and/or poor RV function on imaging. d. Additional imaging or haemodynamic parameters may be required at least in specific populations, such as young patients with typical idiopathic PAH, HPAH or those with CTD-PAH. If non-low-risk imaging and/or haemodynamic parameters exist, reclassification as low-intermediate patients is suggested. e. As per ESC/ERS 3-strata risk stratification. f. Transplant referral should be considered in selected high-risk patients at diagnosis and in intermediate-high or high-risk patients at reassessment. PAH: pulmonary arterial hypertension, IPAH: idiopathic PAH, HPAH: hereditary pulmonary arterial hypertension, CTD: connective tissue disease, CHD: congenital heart disease, ERA: endothelin receptor antagonist, PDE5i: phosphodiesterase-5 inhibitor, ASI: activin signalling inhibitor, PPA: prostacyclin pathway agent, RV: right ventricle, sGCs: soluble guanylyl cyclase stimulator, inh: inhaled, i.v.: intravenous, s.c.: subcutaneous ESC: European Society of Cardiology, ERS: European Respiratory Society.

- Haemoglobin level exceeds the ULN by >2 g/dL, or
- Platelet counts fall below 50×10^9/L.

If treatment is resumed more than 9 weeks after interruption, it should restart at the initial dose of 0.3 mg/kg.

4. CONCLUSION

The treatment landscape for PAH is rapidly evolving, with the activin signalling inhibitor sotatercept emerging as a promising agent for improving patient outcomes. A new treatment algorithm is proposed, grounded in the latest evidence and emphasising the importance of expert opinion and an individualised approach to integrating this novel therapy into clinical practice.

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CONFLICT OF INTEREST

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CORRESPONDING AUTHOR. E-mail: ggiannakoulas@auth.gr.

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