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Trimetazidine in cardiovascular medicine

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ABSTRACT

Abnormalities of myocardial energy metabolism appear as a common background of the two major cardiac disorders: ischemic heart disease (IHD) and heart failure (HF). Myocardial ischemia has been recently conceived as a multifaceted syndrome that can be precipitated by a number of mechanisms including metabolic abnormalities. HF is a progressive disorder characterised by a complex interaction of haemodynamic, neurohormonal and metabolic disturbances. HF may further promote metabolic changes, generating a vicious cycle. Thus, targeting cardiac metabolism in IHD patients may prevent the deterioration of left ventricular function, stopping the progression to HF. For these reasons, several studies have explored the potential benefits of trimetazidine (TMZ), an inhibitor of free fatty acids oxidation that shifts cardiac and muscle metabolism to glucose utilization. Because of its mechanism of action, TMZ has been found to provide a cardioprotective effect in patients with angina, diabetes mellitus, and left ventricular (LV) dysfunction, and those undergoing revascularization procedures, without relevant side effects. In addition, the lack of interference with heart rate, arterial pressure, and most of frequent comorbidities, makes TMZ an attractive option for patients and clinicians as well. The impact of TMZ on long term mortality and morbidity in ischemic syndromes and in heart failure need to be conclusively confirmed in properly designed RCT.

1. Introduction

Ischemic heart disease (IHD) and heart failure (HF) are two major cardiac disorders whose prevalence is increasing, with a huge burden for global healthcare systems. Acute and chronic ischemic syndromes affect about 3 million males and 2.8 million females in Europe and have been traditionally attributed to coronary atherosclerotic obstructions that may abruptly or progressively lead to vessel lumen occlusion [1]. It has recently been acknowledged that, beside atherosclerotic lesions, other mechanisms, such as endothelial dysfunction, microvascular disease, and vasospasm, either isolated or in combination with atheromatous plaques, may precipitate myocardial ischemia [2]. Therefore, IHD is a much more complex syndrome than obstructive atherosclerosis of the coronary arteries [3,4].

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Anti-ischemic strategies are focused on removal of the coronary obstruction and on pharmacological modulation of cardiac work and coronary blood flow. Unfortunately, stenosis focused strategies have a limited and transient impact on symptoms, and no impact on prognosis [5–7].

Recent advances in the understanding of IHD have called attention to strategies that target "alternative pathogenetic mechanisms", including modulators of cardiac energy metabolism [8]. Metabolic modulation may play a major role in acute ischemic events, [9,10], may impact on the results of interventions and may prevent the development of heart failure (HF) [11–12].

Hence, inadequate cardiac energy production as the result of either insufficient substrate availability or insufficient cellular ATP production appears at the crossroad of both IHD and LV dysfunction/HF. Therefore, addressing cardiac metabolic issue in IHD may provide benefits by preventing the deterioration of LV function and stopping the progression to HF [13,14].

With the exception of calcium channel blockers in Prinz-Metal angina, no agent has been tested in angina patients when a flow-limiting stenosis was absent or had been removed, based on the reluctance of cardiologists in accepting a diagnosis of angina in the absence of a flow-limiting stenosis.

Based on these new concepts, drugs of proven clinical efficacy such as trimetazidine (TMZ), an inhibitor of free fatty acids (FFA) oxidation that shifts cardiac and muscle metabolism to glucose utilization resulting into a greater production of high-energy phosphate [13], deserve an objective re-evaluation of their clinical value.

2. Efficacy of TMZ in chronic IHD (stable angina)

Several clinical studies, part of the development program of TMZ, have confirmed its effect to be similar to other anti-angina drugs, including β-blockers and calcium channel blockers. An interesting study, back in 1997 proved the superiority of the combination β-blocker with TMZ versus β-blocker with long-acting nitrate [15].

In this study TMZ was compared with isosorbide dinitrate, both in a combination with propranolol in a double blind controlled study including 53 angina patients. Exercise duration and time to 1-mm ST depression were prolonged in the TMZ group and not in the isosorbide dinitrate group.

In 2003 a meta-analysis confirmed that TMZ in monotherapy or in combination therapy significantly reduces the number of angina attacks and improves stress testing parameters (time to 1-mm ST segment depression, and total work at peak exercise [16]. In that year, a multicentre, double blind, placebo controlled trial was performed to test TMZ modified release (MR) twice daily 35 mg in combination with atenolol in 223 patients with stable angina. The combination of trimetazidine 35 mg bid with atenolol 50 mg prolonged time to 1 mm ST depression, occurrence of angina or exercise test duration in comparison to atenolol in combination with placebo. The study demonstrated anti-anginal and anti-ischemic benefits of trimetazidine at trough with an excellent safety profile.

In 2005 several studies confirmed the efficacy of TMZ in patients with stable angina. One of these studies enrolled 166 patients resistant to nitrates or beta-blockers in a randomized placebo-controlled trial. TMZ, in combination with other antianginal drugs, significantly increased exercise tolerance, delayed angina symptoms onset and prolonged the time to 1-mm ST segment depression during exercise compared to placebo. These results were obtained in the absence of changes in the rate pressure product, confirming again that TMZ could be used in combination with hemodynamic agents [17]. Another study on 279 patients, tested the efficacy of TMZ MR 35 mg twice daily in comparison to TMZ standard release 20 mg three times daily in a primary care practice [18]. TMZ 35 mg MR was more effective than standard TMZ in reducing the angina attacks per week and in decreasing nitroglycerin consumption.

In 2011, a new meta-analysis compared the efficacy of TMZ with other agents that do not affect the heart rate [19]. The meta-analysis included 19,028 patients with stable angina and confirmed that TMZ was comparable to other non-heart rate lowering antianginal drugs in the treatment of stable angina.

Current ESC guidelines on the management of IHD officially categorized TMZ as a drug for symptom relief in patients with stable angina with level of evidence IIb.

In summary, ample evidence supports that TMZ is at least as effective as beta-blockers, nitrates and calcium channel antagonists in increasing exercise tolerance, prolonging time to 1-mm ST segment depression, and in reducing the number of angina attacks and consumption of short acting nitrates.

3. Efficacy of TMZ in acute syndromes

The GISSI study demonstrated the effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Its publication triggered a burst of enthusiasm among Cardiologists that were proposed for the first time with an effective therapy for acute myocardial infarction (AMI). The initial enthusiasm was however tempered by a growing awareness that myocardial reperfusion is a double-edged sword. Reperfusion injury is attributed to the burst of oxygen free radicals which cause lipid peroxidation, enzyme denaturation and direct oxidative damage to cardiomyocytes' DNA. Reperfusion-injury may cause life-threatening arrhythmias, stunning, Microvascular obstruction and cellular death [20].

In the early 90s, the European Union promoted a concerted action to improve the outcome of AMI patients, the European Myocardial Infarction Project-Free Radicals (EMIP-FR). Two were the therapeutic interventions considered in this trial: a thrombolytic agent to restore vessel patency and TMZ to protect the ischemic myocardium from the reperfusion injury [9,10]. In spite of the premature interruption of the study, due to the stop of the production of the thrombolytic agent, the data obtained allowed to demonstrate a beneficial effect of the intravenous form of TMZ in combination with pre-hospital thrombolysis.

In patients treated within 6 h from symptom onset, those receiving i.v. TMZ as an adjunct to primary PCI, had an earlier and more marked return toward baseline of ST deviation [21]. Moreover, in diabetic patients with anterior myocardial infarction treated within 6 h, oral TMZ was associated with a higher rate of complete resolution of ST segment elevation, lower biomarkers peaks, better LV ejection fraction (LVEF) and fewer cardiac adverse events at follow up [22].

A systematic review has concluded that adjunctive TMZ therapy reduces total major adverse cardiac events in AMI patients [23].

In summary, TMZ combines a potent anti-ischemic effect, a marked cardio protective action, in the absence of unwanted effects on heart rate, arterial pressure, and LV contractility. This unique property makes TMZ the ideal agent in acute coronary syndromes, where ischemic damage may be exacerbated by reperfusion injury and patients often present with hemodynamic instability. However, the full potential of TMZ in acute coronary syndromes is yet to be evaluated with properly designed trials.

4. Cardioprotection by TMZ during and after myocardial revascularization

Several studies have explored the potential benefits of TMZ in patients undergoing myocardial revascularization, either by coronary artery bypass grafting (CABG) or PCI.

The ability of TMZ to reduce oxidative stress in cardiac surgery was tested in 24 patients undergoing on-pump CABG. TMZ was given for 2 weeks before surgery and blood samples were collected for measurement of the serum concentrations of major endogenous antioxidant enzyme systems [24]. The results showed that the levels of superoxide dismutase and glutathione peroxidase were higher in TMZ-treated

patients, whereas the level of malondialdehyde was lower than in controls. It is tempting to speculate that TMZ pretreatment may reduce ischemia-reperfusion damage during cardiac surgery [24]. The cardio protection conferred by TMZ has been confirmed by the lower levels of biomarkers of cardiac injury such as myoglobin, troponin T, CK, and CK-MB in patients undergoing open heart surgery pre-treated with TMZ as compared to patients receiving standard care.

Bonello et al. randomized 582 patients with stable angina undergoing PCI, to either an acute loading dose of 60 mg of TMZ or no treatment prior to intervention. Post-procedural cardiac troponin I levels were significantly reduced in the TMZ group, as well as total amount of cardiac troponin I released after PCI [25].

Shehata et al. evaluated the effect of trimetazidine on periprocedural myocardial injury and contrast-induced nephropathy (CIN) in 100 stable angina diabetic patients with mild-to-moderate renal dysfunction. Patients treated with Trimetazidine 35 mg bid had significantly lower cardiac troponin rise and lower rate of contrast induced nephropathy in comparison to the control group [26].

Xu et al. [27] evaluated the effects of TMZ on recurrent angina pectoris and LV function after drug-eluting stent (DES) implantation in 510 elderly diabetic patients with multivessel coronary artery disease and a LVEF of >50%. At 2-year follow-up, patients in the TMZ group showed significant improvements in the incidence and severity of angina pectoris, as well as in the silent myocardial ischaemia and angina pectoris free survival. LV function and structure, non-invasively assessed, in TMZ-treated patients were also stable at 2-year follow-up, whereas, they significantly deteriorated in the control group. These data support the hypothesis that adjunctive therapy with TMZ after DES implantation can have a beneficial effect on recurrent angina pectoris as well as on LV function in elderly patients with diabetes and multivessel coronary artery disease.

Recently, a systematic review and meta-analysis confirmed the myocardial preservation by preoperative TMZ therapy in 402 patients undergoing CABG [28]. The pooled effect sizes showed significantly lower postoperative levels of CK, CK-MB, troponin T and troponin I in the TMZ-treated CABG patients by comparison with control CABG patients regardless of the time the samples were obtained post-CABG.

5. Efficacy of TMZ in diabetics with myocardial ischemic symptoms

In diabetic and pre- diabetic states a reduced glucose uptake and utilization coupled with a preferential FFA oxidation occur as a consequence of inadequate insulin receptor signalling due to either a state of insulin resistance or decreased insulin levels. In diabetic patients, the increased uptake and utilization of FFA both at rest and during stress and ischemia is responsible for the increased susceptibility to myocardial ischemia and to a greater decrease of myocardial performance. When FFA oxidation becomes the almost exclusive source of energy, an intracellular accumulation of lipids occurs –a condition commonly referred as 'Lipotoxicity' for its negative impact on cellular homeostasis and performance. Therefore, a therapeutic approach aimed at an improvement of cardiac energy metabolism through manipulations of substrates utilization is expected to improve myocardial tolerance to ischemia and to preserve LV function.

These expectations have been confirmed in several trials. In 30 diabetic patients with symptomatic and silent ischemia undergoing 24 h Holter monitoring, TMZ reduced the number of episodes of transient silent and non-silent myocardial ischemia, and the total ischemic burden [29].

The favourable effects of TMZ in diabetic cardiomyopathy are independent from change in myocardial perfusion. If anything, the changes in ventricular performance were more evident in patients with more severe perfusion deficits [30].

The cardio protective effect of TMZ in Diabetes Mellitus type 2 patients with AMI, undergoing PCI has been recently confirmed [30]. In 173 diabetic patients undergoing primary PCI, randomized to TMZ on top of standard therapy was shown that TMZ significantly reduces cardiac enzymes rise, improves cardiac and liver function [31].

These observations make TMZ a preferable drug for the management of patients with myocardial ischemia and type 2 diabetes, LVD, or both.

6. Efficacy of TMZ in HF

The myocardial metabolic abnormalities in HF include a decrease in phosphocreatine and ATP levels. Impaired mitochondrial integrity and function are causing a switch from mitochondrial oxidative metabolism to an increase in glucose uptake and glycolysis. Impaired mitochondrial glucose oxidation results in an uncoupling of glycolysis from glucose oxidation and production of lactate and protons, leading to decrease of contractility. TMZ inhibits FFA oxidation and increases glucose oxidation, reducing the production of both lactate and protons, which improves cardiac efficiency. Given the similarities between energy metabolism in cardiac and skeletal muscle, it is not surprising that TMZ also improves skeletal muscle performance [32–35].

Numerous clinical trials in patients with HF with reduced ejection fraction (HFrEF) have demonstrated that TMZ improves symptoms, increases exercise capacity, ameliorates quality of life, preserves LVEF and prevents LV remodelling. The efficacy of TMZ has been confirmed also in idiopathic dilated cardiomyopathy [34]. Four meta-analyses have confirmed the improvement of LV functional capacity, as well as the delay/reversal of the LV remodelling and reduction of B-type natriuretic peptide levels [36].

In one of these meta-analyses, 17 trials with data on 955 patients were identified by literature search [12]. This meta-analysis confirmed the beneficial effects on LVEF, LV volumes, and exercise tolerance that were associated with a significant reduction in all-cause mortality (RR 0.29; 95% CI 0.17 to 0.49; $p < 0.00001$), major cardiovascular events and re-hospitalizations (RR 0.42%: 95% CI 0.30 to 0.58; $p < 0.00001$).

Based on these data, the 2016 ESC guidelines on HF] recommended TMZ for the relief of angina pectoris in patients with HFrEF in combination with a beta blocker or an alternative agent (class IIb, level of evidence A).

Several studies demonstrated a myocardial energy deficit also in patients with HF and preserved EF (HFpEF) [37–39]. Therefore, TMZ may be also considered as an anti-anginal agent in all patterns of HF (HFrEF, mid-range ejection fraction, HFpEF).

Amelioration of Quality of Life with TMZ in HF patients may also reflect the improved performance of the skeletal muscles-an effect well known to professional athletes that could take advantage of the boosting effect of Trimetazidine on skeletal muscles performance. This is the reason why the drug is listed among the doping substances by the International Olympic Committee.

7. Mechanisms of cardioprotection with TMZ

Both myocardial ischemia and HF result in dramatic alterations in cardiac energy metabolism. Mitochondrial oxidative metabolism is compromised during myocardial ischemia (Fig. 1A), as well as in the failing heart (Fig. 1B). This results in an increase in myocardial glycolysis rates as the heart attempts to compensate for the decrease in mitochondrial ATP production (Fig. 1A and B) [40]. Unfortunately, this increase in glycolysis exceeds the subsequent mitochondrial oxidation of pyruvate (glucose oxidation) derived from glycolysis, resulting in the intracellular accumulation of lactate and protons. The protons produced from this uncoupling of glycolysis from glucose oxidation contribute to a disruption in myocardial ionic homeostasis that results in a decreased cardiac efficiency [39]. In both the ischemic heart and the failing heart the remaining mitochondrial oxidative metabolism originates primarily from fatty acid β-oxidation, which occurs at the expense of glucose oxidation. While fatty acids are a plentiful source of energy, they are less

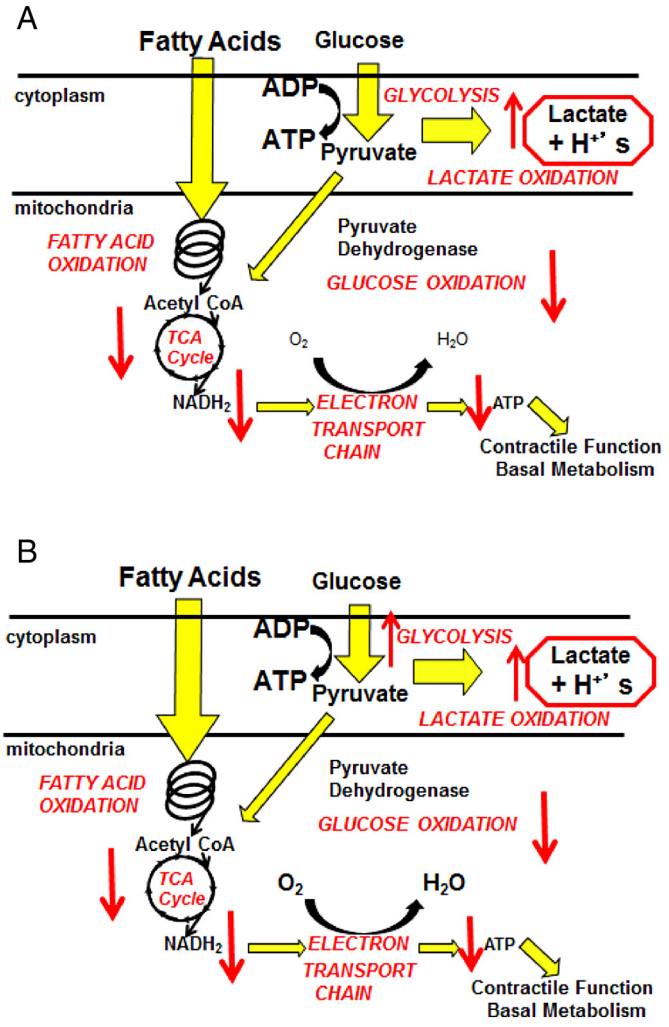

Fig. 1. A–B. Energy metabolism in the ischemic heart and the failing heart. In normal conditions both FFA β-oxidation and glucose oxidation contribute to ATP production. In hypoxic conditions, FFA oxidation is enhanced, so is anaerobic glicolisis, but glucose oxidation is reduced. The uncoupling of glicolisis and glucose oxidation is the biochemical landmark of cellular hypoxia, leading to intra-cellular lactate accumulation, that causes acidosis of the cell. Similarly, in the failing heart overall mitochondrial ATP production decreases due to compromised mitochondrial function. Glycolysis increases in attempt to compensate for the decrease in mitochondrial oxidative metabolism. Of the remaining mitochondrial oxidative metabolism, glucose oxidation decreases to a greater extent than fatty acid β-oxidation. This increases the uncoupling of glycolysis from glucose oxidation, thereby contributing to proton production in the heart.

efficient than glucose ~~oxidation~~, and thereby result in a decrease in cardiac efficiency [40].

The beneficial effects of TMZ in IHD and HF can be attributed to a decrease in cardiac fatty acid β-oxidation (Fig. 2). TMZ is a competitive inhibitor of long chain 3-KAT, the last enzyme of fatty acid β-oxidation [41–42]. The inhibition of 3-KAT results in a decrease in fatty acid β-oxidation, which is paralleled by an increase in myocardial glucose oxidation. The effects of TMZ on myocardial fatty acid β-oxidation rates described in animal models [41–42] have also been observed in the human heart. In patients with HF, improved LVEF following TMZ administration is accompanied by a 10% decrease in fatty acid β-oxidation [33]. The TMZ stimulation of glucose oxidation results in an improved coupling between glycolysis and glucose oxidation, and decreases proton production arising from the uncoupling of glycolysis from glucose oxidation [40]. Consequently, TMZ improves pH and prevents the ionic imbalance that can occur during myocardial ischemia [33], or in the failing heart [43].

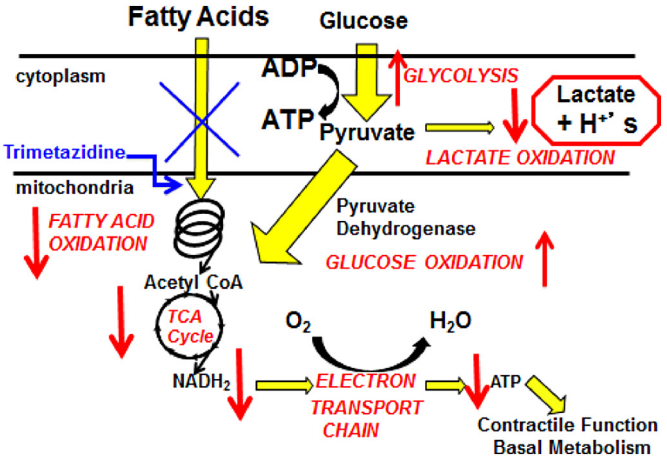

Fig. 2. TMZ inhibition of fatty acid β-oxidation in the ischemic and failing heart increases glucose oxidation and improves cardiac efficiency. TMZ inhibits the fatty acid oxidative enzymes 3-ketoacyl CoA thiolase, thereby decreasing fatty acid β-oxidation and increasing glucose oxidation. This results in a better coupling of glycolysis and glucose oxidation, thereby lessening lactate and proton production and increasing cardiac efficiency.

In addition to its effect on mitochondrial fatty acid β-oxidation, TMZ has also been shown to: i) improve endothelial function by increasing nitric oxide (NO) production, ii) inhibit cell apoptosis, and iii) act as an antioxidant. Whether TMZ exerts these effects by acting directly on the NO, apoptotic or anti-oxidant pathways, or whether these actions are occurring secondary to fatty acid β-oxidation inhibition altering these pathways is not clear. In specific conditions, these actions may contribute to the cardio protective actions of TMZ. In acute ischemic events, including Acute Myocardial Infarction and transient myocardial ischemia either spontaneous or induced by balloon inflation or cardioplegic solution, the free-radical scavenging properties of TMZ may play a relevant role in protecting cardiac cells from ischemia-reperfusion injury [9–10,21,23–26,28].

8. Conclusions

Myocardial ischemia, traditionally perceived as consistently associated with coronary atherosclerotic obstructions is now regarded as a complex syndrome with a number of pathogenetic mechanisms including coronary atherosclerotic obstructions, coronary vasospasm, coronary microvascular dysfunction, and possibly inflammation, endothelial dysfunction and platelet dysfunction [2].

Unfortunately limited evidence is available on medical therapy of these alternative mechanisms, except for coronary vasospasm, that is well controlled in most patients with calcium channel blockers and some recent evidence with ranolazine in microvascular dysfunction [44] and with some anti-inflammatory agents (canakinumab) [44].

Coronary percutaneous revascularization procedures that had triggered high expectations, do not improve prognosis and have a limited and transient impact on symptoms.

Over 61 prospective randomized clinical trials have compared elective PCI with medical therapy and none has shown a significant benefit on mortality and morbidity. Even a most recent meta-analysis concluded that" there was no survival benefit from percutaneous coronary intervention in any subset defined by angiographic or ischemic severity" [45].

In addition to the disappointing impact of elective PCI, a number of recent observations reinforced the central role of medical therapy in the management of chronic myocardial ischemic syndromes, including: 1) The low prevalence of significant stenosis in patients with typical angina and or inducible myocardial ischemia [46,47], 2) The persistence of

symptoms in a large fraction of patients following "successful" PCI [48], and 3) The common underestimation of periprocedural myocardial damage [49].

With this background, medical therapy should be considered as the initial treatment and maintained life-long. Having in mind this long-term perspective, patients' tolerability, absence of relevant side effects, lack of interference with hemodynamic parameters, all become relevant criteria for the choice of the anti-anginal drugs in the individual patient.

Comorbidities, including diabetes, chronic obstructive pulmonary disease, peripheral artery disease, LV dysfunction, hypotension/hypertension, bradycardia/tachycardia, cognitive disorders, frailty, etc. are very common in ischeming as well failing patients and need be taken into consideration when choosing treatment.

TMZ, a metabolic modulator, is effective independently of the mechanism precipitating myocardial ischemia. It is well tolerated and does not interfere with heart rate, arterial pressure, atrioventricular conduction, cardiac contractility, vascular tone, and brochial contraction. These unique properties render TMZ an attractive option for angina patients, including diabetics, patients with LV dysfunction, and patients with severe comorbidities in monotherapy or in combination with other drugs.

Contributors

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MM has received honoraria from Servier and Menarini for speaking. MM has received honoraria from Servier for steering committee membership, and consulting.

DV received honoraria from Servier, Novartis, Pfizer, Bayer, Boehringer Ingelheim, Mylan, for speaking and consulting. Support for Research from Servier, Amgen, Astra Zeneca, Novartis, and Johnson & Johnson.

YC has received honoraria from Servier for speaking.

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JJD has received honoraria from Serdia India, for steering committee meeting and consulting.

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EET has received honoraria from Servier for speaking.

RF has received honoraria for steering committee membership and consulting from Novartis and Servier; and for speaking and support for travel to study meetings from Amgen, Bayer, Boehringer Ingelheim, Merck Serono, and Servier.

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