

Expert Perspective

Medical Management of Stable Angina

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Key words: **Stable angina, medical management, statement, Hellenic Cardiovascular Research Society.**

The following statement represents the work of a panel of experts that was organized by the Hellenic Cardiovascular Research Society. Disclosure information for members of this panel is included in the appendix at the end of the manuscript.

It is important to clarify that this statement applies to patients who present with stable angina in the setting of inability to benefit further from revascularization, if revascularization is either not indicated or not feasible. In this context, the issue of diagnostic and therapeutic procedures related to the invasive management of ischemic heart disease will not be discussed.

The scientific background that influenced the position of the committee, apart from articles published in the literature, was formed by the 2006 guidelines of the European Society of Cardiology on the management of stable angina pectoris,¹ the 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines for the diagnosis and management of patients with stable ischemic heart disease,² and the recently published NICE guidelines on stable angina.³ The scope of the committee was to evaluate the role of novel therapeutic strategies aiming to reduce symptoms and improve prognosis, and to adjust available evidence

and recommendations to the characteristics of patients with stable angina in the Greek population, as well as to formulate recommendations that would take into consideration the special characteristics of the local national health system.

Introduction

Despite the remarkable advances in cardiovascular therapeutics, and specifically in the invasive therapy of ischemic heart disease, the prevalence of stable angina in the industrialized world is considerably high. It is well-known that stable angina increases the risk for subsequent cardiovascular events and imposes a considerable burden on the quality of life of affected patients. Finally, patients with stable angina present increased morbidity and hospitalizations, increasing the economic cost of ischemic heart disease for the health payers.^{4,5}

Definition

According to the ESC guidelines for the management of stable angina,¹ “stable angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exer-

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tion or emotional stress and relieved by rest or nitroglycerin." In the vast majority of cases this broad definition refers to a clinical syndrome that is caused by myocardial ischemia. In most of the cases of myocardial ischemia the underlying cause is atherosclerotic coronary artery disease (CAD); thus, the therapeutic management of stable angina discussed in this document is focused mainly on ischemic heart disease. A minority of patients with anginal symptoms on exertion may also present with vasospastic/variable angina (Prinzmetal angina) or syndrome X. Although atherosclerotic coronary artery disease is often present, the differences in the pathophysiology and treatment of these forms of angina do not allow the extrapolation of the following recommendations to these patients.

Epidemiology

The prevalence of angina in European populations increases with age. It is quite infrequent in individuals aged 40-50 (<1%) but it may reach 10-20% in patients aged >70 years. In addition, the incidence of angina has been reported to be about 0.5%, but we have to take into consideration that the prevalence varies considerably between populations and that most of the data were derived by studies conducted more than 10 years ago.⁶⁻⁹

Indeed, the incidence of myocardial infarction (MI) has declined in countries with advanced health systems, mainly because of the beneficial results of preventive measures at the population level. However, even in these countries, the prevalence of stable angina has not decreased accordingly, despite the wider availability of reperfusion therapies. This is mainly attributed to the demographic changes of the populations in the industrialized world.¹⁰ Recent epidemiological data from the Greek population are sparse. In a recent telephonic survey study, it was reported that the prevalence of angina in a Greek population of 3007 adults (aged 47 ± 16 years, 48.3% men and 51.7% women) was 2.5%.¹¹ Thus, stable angina remains an important clinical issue with profound effects on the quality of life and long-term prognosis of our patients.

Management of stable angina

Clearly, non-pharmacological preventive measures should be considered the cornerstone of the management of patients with stable angina. In particular,

cessation of cigarette smoking and individualized adjustment of exercise level are of utmost importance. Furthermore, the treatment goals of the Fifth Joint Task Force of the European Society of Cardiology on cardiovascular disease prevention in clinical practice (e.g. goals regarding appropriate lipid levels and hypertension) should be considered mandatory for patients with ischemic heart disease and stable angina.¹² It should be clear that, although this paper is focused on the pharmacological management of ischemia in patients with stable angina, the aforementioned preventive measures should be the first and possibly the most important step in the management of all patients with ischemic heart disease.

Pharmacological management of stable angina

1. Beta-blockade therapy

Beta-blockers improve ischemia and symptoms mainly by reducing oxygen consumption. The protective anti-ischemic effects afforded by beta-blockade therapy are mostly mediated by beta-1 adrenoceptor blockade. The beta-1 selective beta-blockers metoprolol (target dose 100 mg bid), atenolol (target dose 100 mg od or 50 mg bid), and bisoprolol (target dose 10 mg od) have been used extensively for stable angina. These drugs are not only supported by a considerable body of experience and evidence accumulated during the last decades, but in addition they present improved tolerability among patients with asthma or chronic obstructive pulmonary disease (COPD). However, in a recently published multicenter study in Greece, the RYTHMOS trial, it was shown that in patients with COPD and ischemic heart disease, carvedilol was the most commonly used beta-blocker, despite the lack of beta-1 selective properties.¹³

Beta-blockers have been proved to reduce morbidity in patients with ischemic heart disease and prior MI.¹⁴ A solid body of evidence has also been created relating to patients with heart failure and ischemic heart disease. Although there is no doubt that beta-blockers improve symptoms and increase the ischemic and arrhythmic threshold in a variety of clinical settings, data on potential mortality benefit are consistent only for patients with prior MI and/or systolic dysfunction of the left ventricle (LV).¹⁵ Thus, beta-blockers are the preferred agents for the treatment of angina in patients with LV dysfunction after MI and in patients with heart failure, because of reverse remodeling and improved survival. The reservations

about the prognostic effects of beta-blockers were first raised by a meta-analysis of atenolol in hypertension, which surprisingly showed that atenolol may actually be associated with a worse prognosis in comparison to angiotensin II receptor blockers and Calcium channel blockers.¹⁶ Moreover, the results of a longitudinal, observational study of 18,653 patients who had been enrolled in the Reduction of Atherothrombosis for Continued Health (REACH) registry and had been followed for 44 months were published recently.¹⁷ According to the results of this large cohort of patients with either CAD risk factors only, known prior MI, or known CAD without MI, the use of beta-blockers was not associated with a lower risk of composite cardiovascular events. In terms of principles, the results of this study should be verified by a specifically designed prospective trial in order to dramatically change our therapeutic strategy. However, such a study is unlikely to be conducted in the near future. One assumption that is difficult to reject or verify would be that, nowadays, the management of patients with ischemic heart disease is entirely different to the management that was available 10 to 30 years ago. Thus, data from small trials conducted in the past should not be extrapolated to all our patients who may benefit from advanced medical care. Finally, the main and growing problem of our patients today is the increased cardiometabolic risk associated with obesity and diabetes mellitus. This fact is particularly relevant to the Greek population.^{18,19} One of the reasons that may be associated with the lack of prognostic benefit from older beta-blockers is their documented unfavorable effects on glucose metabolism.²⁰ However, whether the higher incidence of diabetes amongst patients receiving beta-blockers counterbalances any potential beneficial effects afforded by beta-blockade therapy in patients with stable coronary artery disease remains to be proved.

In conclusion, despite the paucity of reliable survival data in the majority of patients who are amenable to treatment with beta-blockers in everyday clinical practice, beta-blockers are rightfully the cornerstone of anti-ischemic therapy in patients with stable angina.

2. Calcium channel blockers

Calcium channel blockers (CCBs) reduce angina by inhibiting inward calcium currents through the cell membrane in many tissues, including the myocardium, cardiac conduction tissues, and vascular smooth

muscle cells in both coronary arteries and peripheral vessels.

The most commonly used CCBs for the treatment of stable angina in Greece are amlodipine, diltiazem, felodipine, verapamil and nifedipine. CCBs constitute an inhomogeneous group of drugs. Diltiazem and verapamil slow heart rate and reduce myocardial contractility, while the dihydropyridines (nifedipine, amlodipine, and felodipine) may cause sympathetic activation, which increases heart rate. Sympathetic activation may partly counterbalance the antianginal effects of CCBs; thus, the management of heart rate through other medications may be warranted in patients receiving dihydropyridines.

The antianginal effects of CCBs have been proved in many studies and are considered to be comparable to those achieved by beta-blockade therapy. In addition, CCBs have been extensively used for the management of hypertension. However, there has been no evidence for any prognostic beneficial effects of CCBs in patients with stable angina. Furthermore, in one study high doses of short-acting nifedipine resulted in increased mortality.²¹ The ACTION study evaluated the prognostic role of CCBs in patients with stable angina and rejected the hypothesized unfavorable effects of nifedipine on prognosis, presenting neutral results.²² However, the majority of the 7665 patients enrolled in ACTION were hypertensives; thus, we may hypothesize that the beneficial effects from the management of hypertension, afforded by nifedipine, were neutralized by its potential unfavorable effects on ischemic cardiovascular outcomes. Finally, clinicians should be aware that CCBs have been documented to increase the risk of heart failure in a number of studies.²³⁻²⁵

3. Nitrates

The role of long-term nitrates has been evaluated in a number of studies, both in patients with stable angina and in patients in the post acute MI period. Nitrates have been proved to reduce angina attacks, increase exercise tolerance, and thus improve the quality of life, especially in the case of limiting angina. However, there are no data supporting the notion that nitrates may confer any mortality or morbidity benefit in patients with stable angina.²⁶⁻²⁸

Although these data are acknowledged by the ESC guidelines² and are well-known to the majority of cardiologists, nitrates are overused in patients with stable ischemic heart disease in Greece, prob-

ably because of their low cost and wide availability.¹⁹ This observation has been verified in a number of surveys that have been conducted in the Greek population.³⁰ The use of both short- and long-term nitrates has been associated with headaches, flushing and hypotension. A well known limitation of the long-term use of nitrates is the phenomenon of nitrate tolerance, which occurs when there is no nitrate-free period. Patients should be aware that transdermal nitrates should be removed during sleeping hours while oral nitrates should be administered preferably once daily in the morning.

Short-acting nitrates are still of clinical importance, despite the lack of prognostic effects, because they improve quality of life and allow increased physical activity in patients with stable angina. However, patients should be aware of the following:

- a. Hypotension may occur if rapid onset nitrates are used in the postural position.
- b. Patients under treatment with long-acting nitrates may not respond as expected to short-acting nitrates, because of the nitrate tolerance phenomenon.
- c. Nitroglycerin spray may be preferable to tablets, which are susceptible to decay and are pharmacologically unstable when exposed to air.
- d. If angina persists despite appropriate use of short-acting nitrates, the patient should be considered at risk for an acute ischemic event and should act accordingly.

4. Ivabradine

Ivabradine is a relatively novel heart rate lowering drug, which inhibits the cardiac pacemaker current I_f . Ivabradine is the only drug of its class available, although other substances with the same mode of action have also been investigated.³⁰ Although its pathophysiological properties are still under investigation, ivabradine is considered to mediate its therapeutic effects exclusively through the heart rate lowering action, which is afforded through the inhibition of the I_f channels located within the sinus node. Thus, ivabradine should not be considered as a therapeutic option in patients with atrial fibrillation or in patients with clinically evident sinus node dysfunction.

The European Medicines Agency (EMA) has approved the use of ivabradine for the symptomatic treatment of chronic stable angina pectoris in adults with CAD who are in normal sinus rhythm, but are unable to tolerate or have a contraindication to the

use of beta-blockers, or in combination with beta-blockers in patients who are inadequately controlled with an optimal beta-blocker dose and whose heart rate is >60 /min. Recently, the EMA approved the use of ivabradine in patients with chronic heart failure NYHA classes II to IV and systolic dysfunction, who are in sinus rhythm and whose heart rate is ≥ 75 /min, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

The anti-ischemic effects of ivabradine have been evaluated in a number of studies, including head to head comparison with beta-blockers and CCBs. Most importantly, its additive anti-ischemic action has been verified on top of the abovementioned therapies.³¹ Interestingly, ivabradine was shown to double the prolongation of exercise time for an equal drop in heart rate when compared with 100 mg atenolol.³² The hypothesized mechanism for these differential effects in response to the same change in heart rate is possibly the underestimated alpha-adrenergic vasoconstriction of the coronary arteries as a result of beta-blockade therapy.³³

The two landmark large-scale randomized trials that have proved the beneficial effects of ivabradine in patients with ischemic heart disease and in patients with heart failure are the BEAUTIFUL trial³⁴ and the SHIFT trial,³⁵ respectively. Briefly, BEAUTIFUL enrolled 10,917 patients who had CAD and an LV ejection fraction $<40\%$. The patients were enrolled if resting heart rate was ≥ 60 /min and were followed for 19 months. The study concluded that the reduction in heart rate with ivabradine does not improve cardiac outcomes in all patients with stable CAD and LV systolic dysfunction, but it reduced the incidence of CAD outcomes in the patients who had baseline heart rate ≥ 70 /min. Furthermore, in patients with angina, the primary endpoint (composite of cardiovascular mortality or hospitalization for fatal and nonfatal myocardial infarction or heart failure) was reduced by 25% (HR=0.76, 95% CI=0.58–1.00, $p=0.05$). In patients with angina and resting heart rate ≥ 70 /min the primary endpoint was reduced by 31%.

The SHIFT study enrolled 6558 patients (mean follow up 22 months) who had symptomatic heart failure and an LV ejection fraction of 35% or lower, were in sinus rhythm with heart rate ≥ 70 /min, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a beta-blocker if tolerated. The primary endpoint was significantly reduced among

patients randomized to ivabradine (HR=0.82, 95% CI=0.75–0.90, $p<0.0001$). The results were mainly driven by the reduction of hospital admissions for worsening heart failure.

Overall, ivabradine has a favorable safety profile. The most common adverse event associated with the use of ivabradine is bradycardia. In the BEAUTIFUL study, 6% of the patients in the ivabradine group presented a heart rate <50 /min and discontinued study medication as required by the study protocol. However, only 23% of these patients were symptomatic. Furthermore, 37 patients (0.3%) withdrew because of visual symptoms such as phosphenes, blurred vision, and visual disturbance (ivabradine 0.5%, placebo 0.2%); these symptoms disappeared after treatment discontinuation.

5. Ranolazine

Ranolazine is a piperazine derivative that in therapeutic concentrations inhibits the late inward Na^+ current, preventing intracellular Ca^{++} overload. In terms of pathophysiology the anti-ischemic and antiarrhythmic effects of ranolazine are profound in cases of ischemia and/or hypoxia, where the role of the late inward Na^+ current is more important and significantly affects the contractile status and energy consumption of myocardial cells.^{36,37}

According to the EMA, ranolazine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).

Ranolazine, in comparison to 100 mg of atenolol, has been shown to cause a similar increase in time to onset of angina and time to 1 mm ST-depression, while it increases exercise duration.³⁸ Ranolazine has also been shown to increase myocardial blood flow, as detected by serial automated quantitative myocardial perfusion imaging techniques.³⁹ In patients with ischemic heart disease, 4 major randomized, placebo-controlled trials, comprising data from 8129 patients, have been published. Three of these studies (MARISA, CARISA and ERICA) have verified the anti-ischemic effects of ranolazine as monotherapy and as add-on therapy to beta-blockers and CCBs.⁴⁰⁻⁴² A common finding in these 3 studies is that the number of anginal episodes and the need for use of short-acting nitrates was reduced by 25% to 35% in the ranolazine group.

The MERLIN-TIMI 36 trial evaluated the role of ranolazine in 6560 patients with unstable angina or non ST-elevation MI (NSTEMI), regardless of the presence of angina.⁴³ The patients were randomized to ranolazine or placebo and were followed for a median interval of 348 days. Although the primary endpoint (cardiovascular death, MI, or recurrent ischemia) was not significantly reduced in the total study population, it was less frequent with ranolazine among the 3565 patients with prior chronic angina (HR: 0.86; 95% CI: 0.75 to 0.97; $p=0.017$), the difference being due entirely to a significant reduction in recurrent ischemia (HR: 0.78; 95% CI: 0.67 to 0.91; $p=0.002$).⁴⁴ In addition, data from MERLIN-TIMI 36 showed that ranolazine significantly improved HbA(1c) and recurrent ischemia in patients with diabetes mellitus and reduced the incidence of increased HbA(1c) in those without evidence of previous hyperglycemia.⁴⁵

Although the pathophysiological mechanism underlying the anti-ischemic effects of ranolazine, and specifically the reduction of intracellular Ca^{++} overload, is fundamental for the mechanisms underlying arrhythmogenesis, the results of the MERLIN-TIMI 36 trial regarding the antiarrhythmic effects of ranolazine were rather unexpected. Briefly, ranolazine significantly reduced the incidence of non-sustained ventricular tachycardias and of supraventricular tachycardias in general. Moreover, there was a trend toward reduced occurrence of new-onset atrial fibrillation (1.7% versus 2.4%, $p=0.08$).⁴⁶ A number of small studies have verified the antiarrhythmic properties of ranolazine. Ranolazine has been shown to reduce the incidence of ventricular arrhythmias in patients with ICDs,⁴⁷ to prevent atrial fibrillation after coronary artery bypass grafting,⁴⁸ to facilitate electrical cardioversion in cardioversion-resistant patients,⁴⁹ and to facilitate pharmaceutical cardioversion of recent-onset atrial fibrillation.⁵⁰ The antiarrhythmic properties of ranolazine are under investigation in specifically designed large-scale randomized trials, which are expected to provide evidence for a future antiarrhythmic indication.³⁷ Meanwhile, we should take into consideration that ranolazine not only has exhibited no proarrhythmic action in clinical trials, but also has been shown to reduce the ventricular and supraventricular arrhythmic burden in patients with stable angina and in patients after unstable angina or NSTEMI. In particular, no proarrhythmic effects were observed in 3162 patients treated with ranolazine, based on 7-day Holter monitoring in the MERLIN-TIMI 36 study.

Ranolazine has a favorable safety profile; common side effects associated with its use are dizziness, headache, constipation, vomiting and nausea.

Algorithm for pharmacological management of patients with stable angina aiming to reduce symptoms and ischemia

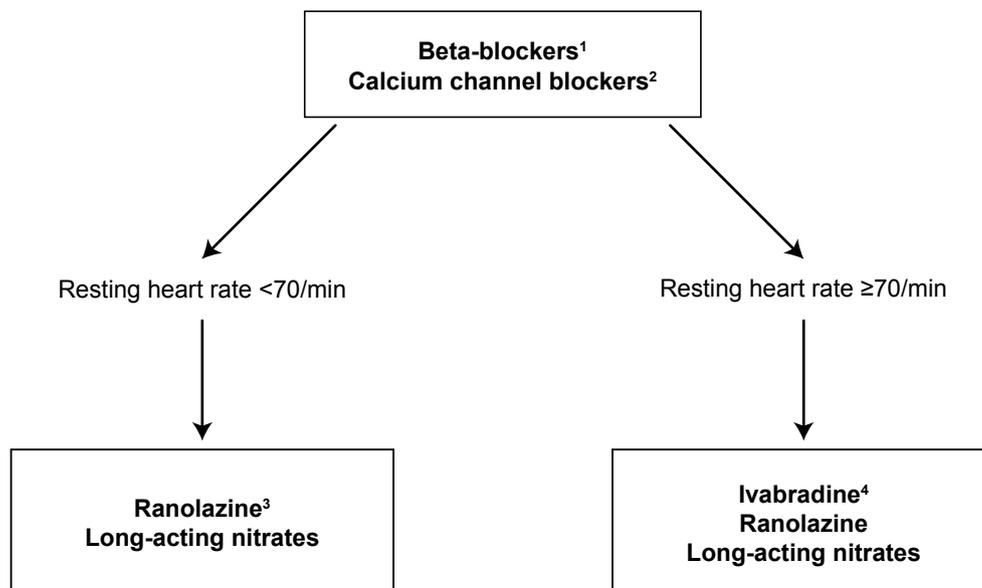
In Figure 1 we have summarized the recommendations of the group for the medical management of patients with stable angina, aiming to reduce symptoms and ischemia. In this article we have evaluated the role of beta-blockers, CCBs, nitrates, ivabradine and ranolazine. The committee members do recognize that there are other antianginal treatments that have been included in other guidelines (e.g. nicorandil in the recent NICE guidelines for stable angina).³ However, medications not included in this paper are not approved by the EMA for this indication, not available in Greece, or not supported by the body of evidence and/or experience from extended clinical use.

We consider the use of short-acting nitrates of

profound importance for patients with frequent angina episodes, mainly because of the increase in exercise tolerance.

Beta-blockers and CCBs remain the cornerstone in the management of patients with stable angina. These drugs are widely available, are affordable, and have accumulated long-term clinical experience among physicians. However, beta-blockers and CCBs represent two inhomogeneous groups of substances with variable therapeutic properties. The clinician should be aware of their strengths and limitations and individualize therapy. With regard to beta-blockade therapy, clinicians should know that, although atenolol and metoprolol have been most studied in ischemic heart disease, nowadays carvedilol and nebivolol are largely used, in view of their more favorable metabolic effects and despite the lack of data from specifically designed trials. This is a plausible therapeutic strategy, given that cardiometabolic risk is a major contributor to coronary risk in Greece.¹⁸

If patients remain symptomatic despite receiving the optimal dosage of beta-blockers and/or CCBs,



1. Short-acting nitrates can be used when needed with all the following medications. However, their efficacy may be reduced in patients receiving long-acting nitrates.
2. Prefer in case of hypertension, avoid in case of heart failure due to systolic dysfunction of the left ventricle. If calcium channel blockers are contraindicated or not tolerated, follow the heart rate-based algorithm.
3. Prefer in cases of atrial fibrillation.
4. Only for patients with sinus rhythm, prefer in cases of systolic heart failure.

Figure 1. Algorithm for the pharmacological management of patients with stable angina, aiming to reduce symptoms and ischemia.

we recommend the use of ranolazine and ivabradine. The key word in everyday clinical practice is “optimal”. It is well-known that the dosage of beta-blockers used in Greece is lower than the evidence-based dosages that have been used in clinical trials.¹³ Clinicians should titrate to the maximum tolerated dosage of beta-blockers before adding new medication.

According to our algorithm (Figure 1) the choice between ranolazine and ivabradine should be largely based on baseline heart rate. We chose the cutoff value of 70 /min because, in the BEAUTIFUL trial, ivabradine improved prognosis only in patients with a resting heart rate ≥ 70 /min. Of course, one could argue based on the fact that EMA has approved ivabradine for patients with a heart rate >60 /min. However, there are no beneficial effects derived from ivabradine in patients with heart rate <70 /min. Furthermore, the EMA approval was released before data from BEAUTIFUL were available. In addition, grouping of patients based on 70 /min was a pre-specified endpoint in the BEAUTIFUL trial. We also have to admit that BEAUTIFUL enrolled only patients with systolic dysfunction, but it is reasonable to extrapolate its findings because of the large number of smaller studies that have been conducted in patients with stable angina who did not have systolic dysfunction. Finally, patients with systolic heart failure are more likely to benefit from ivabradine (SHIFT study) and should avoid the use of CCBs.

In patients with heart rate <70 /min, in those with sick sinus syndrome, and in those with atrial fibrillation, ranolazine should be considered the drug of choice. Ranolazine has well-documented antianginal efficacy in combination with beta-blockers and/or CCBs. Notably, the prognosis of patients with a history of angina was improved in the MERLIN-TIMI 36 trial. In addition, ranolazine is well tolerated and may reduce the incidence of supraventricular (including atrial fibrillation) and ventricular tachycardias.

Long-acting nitrates remain an affordable and widely available therapeutic option. However, long-acting nitrates lack any favorable prognostic effect; thus, their use should focus solely on improvement of symptoms.

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Appendix

Disclosure information

GA: Research grants, honoraria for lectures and advisory boards on ischemic heart disease treatment from: Astra, Boehringer, Elpen, Roche, Menarini, MSD, Pfizer, Servier.

JP: Research grants from Abbott USA, Orion Pharma Finland, Honoraria for lectures from Menarini International

GF: None related to this subject. Research Grants or Advisory: European Union, Alere, Cothera, Bayer, Nanosphere

MN: None

KP: None

VV: None related to this subject

KK: Modest teaching fees from Pfizer, Menarini & Actelion

DA: None related to this subject. Modest honoraria for lecturing from AstraZeneca

JG: None