Orthostatic arterial hypotension
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DEFINITION
Orthostatic arterial hypotension (OhTN) is defined as “a progressive and sustained fall in systolic blood pressure (SBP) from baseline value ≥20 mmHg or diastolic blood pressure (DBP) ≥10 mmHg, or a decrease in systolic blood pressure to <90 mmHg” when transitioning from the supine to the upright position¹. In those with a SBP >160mmHg when supine, OhTN is defined as a fall in SBP of at least 30mmHg²,³. The current definition does not include the 3 minutes time of BP drop as criteria for the diagnosis, introduced in 1996 by the OhTN definition Consensus¹, but it is currently considered as part of the classical OhTN picture. The reason for excluding this criteria is a consequence of studies which have shown that OhTN during passive orthostatism at the tilt test may develop late, between 3 and 15 minutes in 15% of cases, and even after 16 minutes in 39% of cases⁴. Clinical studies have shown that OhTN occurs late after active orthostatism in >50% of patients with neurologic conditions⁴, and evolves to classical OhTN during the course of the following 10 years in 50% of patients⁵. Using devices that measure BP and heart rate simultaneously in patients with symptoms during the first minute of orthostatism consistent with OhTN, an initial OhTN was described when a drop in SBP of at least 40 mmHg and in DBP of at least 20 mmHg during the first 15 seconds, with a recovery in the following 30 seconds⁷.

PREVALENCE
Studies providing prevalence data have mainly assessed classical OhTN and show significant variability according to age, comorbidities, and associated medication. It was reported in <5% of subjects <65 years⁸, in 20% of those >65 years⁹, in 30% of those >75 years¹⁰, in >50% of institutionalized elderly fragile subjects¹¹, and in 64% of elderly admitted patients¹². It was frequently associated with medication – vasodilatator drugs and tricyclic antidepressants, and with alcohol consumption¹³. Orthostatic hypotension was reported in 23-50% of patients with Parkinson’s disease¹⁴, and in 20% of patients with type 2 diabetes mellitus¹⁵. Symptomatic forms of OhTN are slightly less frequent than asymptomatic ones, and are reported in 2% of subjects <65 years⁹, and 16% of those suffering from Parkinson’s¹⁶.

PATHOPHYSIOLOGY
OhTN is a consequence of the inefficiency of compensatory mechanisms to correct BP when transitioning to an upright position. Gravitation redistributes 500-1000 ml of blood to the subdiaphragmatic vascular bed with the change from clino to orthostatism, which in turn leads to relative hypovolemia followed by a reduction of ~40% in stroke volume and a decrease in arterial pressure during the first moments of orthostatism. The decrease in arterial pressure stimulates the sympathetic nervous system and diminishes the intervention of the parasympathetic nervous system by stimulating baroreceptors of the carotid sinus and the aortic arch¹⁷. Sympathetic reference further stimulates autonomous centers in the central nervous system which includes hypothalamic centers, the solitary nucleus, medulla oblongata and medullar centers, which further transmit the impulse through afferent fibers to release norepinephrine (NE) in the preganglionic and postganglionic synaptic cleft. This postganglionic NE release leads to systemic and splanchnic vasoconstriction, and increased inotropism and heart rate which restores arterial pressure affected by the relative orthostatic hypovolemia¹⁸. Posture related hemodynamic changes are usually accompanied by increased NE plasma levels. The release of NE is reduced in the postganglia segments in OhTN associated with central or peripheral nervous system disorders such as multiple

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OhTN is caused by primary neurogenic conditions which affect the central and peripheral autonomous nervous system. The nervous system is damaged by deposits of α-synucleoprotein occurring in the central and peripheral autonomous nervous system. The mechanism underlying synucleinopathy associated OhTA is the decrease in postsynaptic NE release, evaluated by the reduction of NE blood levels which has been useful in clinical practice in neurology to guide the OhTN therapy specific for these cases. Unlike for this patient subset, in those with MSA, who indeed associate OhTN in 70 – 80% of cases, the initial peripheral residual sympathetic tonus and near-normal NE blood levels are preserved. PAF and MSA are the most frequent etiologies for OhTA of the middle aged and elderly patients. In the elderly, OhTN secondary to autonomous nervous system dysfunction/injury can be amplified by vascular disease (increased arterial stiffness) or cardiac disease (chronotropic incompetence and myocardial stiffness) associated with a reduction in vasoconstrictive, chronotropic, and inotropic response to NE.

Postprandial hTN has been reported in 37% of patients with OhTN, occurring through unclear mechanisms, which may involve sympathetic baroreflex dysfunction, the release of vasodilating intestinal peptides, and the increased postprandial blood flow in the splanchnic vascular bed.

CAUSES

OhTN associated with neurologic conditions affecting the central or peripheral autonomous nervous system (synucleinopathies: PD, PAF, MSA, LBD) is considered a result of primary neurogenic causes. OhTN associated with peripheral autonomous nervous system dysfunction/injury in the setting of chronic diseases such as diabetes, amyloidosis, neoplasia, or autoimmune diseases (Guillain-Barre syndrome), chronic renal disease, metabolic diseases (porphyria, Fabry disease, vitamin B deficiency, alcoholism), trauma or medullary iatrogenic lesions (sympathectomy), infections (HIV, botulism, etc.) is considered a result of secondary neurogenic causes, also denoted non-neurogenic causes (Table 1).

In the setting of a normal autonomic function, OhTN can be the consequence of absolute hypovolemia (post-hemorrhagic, severe dehydration, adrenal failure, cardiac failure under excessive diuretic therapy) or of excessive iatrogenic vasodilation (vasodilator-induced)

Table 1.

<table>
<thead>
<tr>
<th>OhTN Causes</th>
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<tbody>
<tr>
<td>Neurogenic</td>
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<tr>
<td>Parkinson disease</td>
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<tr>
<td>Multiple system atrophy</td>
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<tr>
<td>Pure autonomic failure</td>
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<tr>
<td>Lewy body dementia</td>
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<tr>
<td>Non-neurogenic</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Chronic kidney disease</td>
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<td>Amyloidosis</td>
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<td>Guillain Barre syndrome</td>
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<td>Paraneoplastic syndromes</td>
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<td>Autoimmune diseases (autoimmune autonomic ganglionopathy)</td>
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<td>Infections (HIV, botulism etc..)</td>
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<tr>
<td>Metabolic causes (B12 vitamin deficiency, alcoholism, porphiria, Fabry disease)</td>
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<tr>
<td>Drugs (vincristine)</td>
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<td>Intoxication (heavy metals etc..)</td>
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<tr>
<td>Trauma (medulla, iatrogenic - sympathectomy)</td>
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<td>Volume depletion</td>
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<td>Bleeding</td>
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<td>Dehydration (diarrhea, vomiting, diuretics)</td>
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<tr>
<td>Relative hypovolemia (venous pooling, heart failure)</td>
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<tr>
<td>Drug induced</td>
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<tr>
<td>Antihypertensives [alpha blockers, alpha 2 agonists, vasodilators (hydralazine, minoxidil), diuretics]</td>
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<tr>
<td>Vasoactive drugs (nitrates, Phosphodiesterase inhibitors type 5)</td>
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<tr>
<td>Antidepressants (tricyclic agents: amitriptyline, nortriptyline, imipramine)</td>
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<tr>
<td>Drugs for Parkinson’s Disease: dopaminergics (levodopa, dopamine agonists), anticholinergics.</td>
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CLINICAL PRESENTATION

The symptoms of OhTN are polymorphic, have low specificity and include vertigo, dizziness, blurred vision, thoracic pain, oftentimes cervical pain. They are a result of sudden transition from clino to orthostatism and may be more frequent during the night in patients with nocturnal diuresis or those administering medication before bedtime (antihypertensive drugs, neuroleptics, alpha-blockers). The nocturnal rise in BP levels increases glomerular arterial pressure, diuresis and natriuresis, leading to morning hypovolemia and an increased risk of morning OhTN\textsuperscript{26}.

OhTN is the identified cause of syncope in 15\% of cases\textsuperscript{27}. Orthostatic syncope is confirmed by the simultaneous drop in BP levels\textsuperscript{1}. The symptoms are influenced mainly by the orthostatic BP levels, and much less by the amount of pressure drop\textsuperscript{1}. OhTN leads to a syncope when SBP drops under 75 mmHg, the cerebral autoregulation pressure threshold.

The symptoms of OhTN in synucleinopathies are associated to the clinical manifestations of the main neurologic condition – motor dysfunction, autonomic dysfunction (OhTA, postprandial hTA, supine HTN, gastrointestinal dysfunction, urogenital dysfunction) and to cognitive decline\textsuperscript{18}. PAF resulting from the predilect deposition of \(\alpha\)-synuclein in the postganglia segment can be considered a human model for OhTN, as the motor component seen with other synucleinopathies is absent in PAF. In PAF forms exclusively/predominantly associating postganglia lesions, the postganglia release of NE and its plasma levels are decreased and do no increase with orthostatism\textsuperscript{28}. MSA, due to the initial depositions of \(\alpha\)-synuclein predominantly in the oligodendroglia of the central nervous system, associates Parkinson-like and cerebellar manifestations. When OhTN is seen at the onset of MSA it is often long-standing\textsuperscript{6}. In PD, OhTN was reported in 20 – 50\% of patients, asymptomatic in 18\% of cases, frequently associated with long-standing severe PD. It may be aggravated by levodopa or vasodilator drugs\textsuperscript{29}. LBD is characterized by the association between cognitive decline and autonomic dysfunction, including OhTN, which significantly reduces survival\textsuperscript{30}.

Postprandial hTN, occurs 2 hours after a meal, more frequently in the first 30-60 minutes, upon assuming the upright position, especially after a heavy meal, hot foods, high on carbohydrates, after alcohol consumption, often on top of the use of psychotropes or diuretics\textsuperscript{22}. It is more frequent in patients with diabetes, PD or Alzheimer’s dementia\textsuperscript{31}.

DIAGNOSTIC

Active orthostatism with SBP drop of at least 20 mmHg and/or a DBP drop of at least 10 mmHg, by sphygmanometry, during the first 3 to 10 minutes of orthostatism following 5 minutes of clinoostatism is diagnostic for orthostatic hypotension\textsuperscript{1}. Heart rate increases in those non-neurogenic OhTN (>15 beats per minute) and shows little variation in those with neurogenic OhTN (<10 beats per minute)\textsuperscript{1,6,32}.

Ambulatory blood pressure monitoring (ABPM) shows a non-dipper pattern in those with OhTN, especially morning OhTN, a pattern frequently seen in those with neurological pathology and dysautonomia, in patients with diabetes, chronic kidney disease, or the elderly\textsuperscript{33}.

Tilt testing is recommended when: 1) OhTN has a daytime variation which does not allow an office diagnosis, 2) there is a clinical suspicion of orthostatic syncope in those with motor anomalies that do not allow for „active orthostatism“ (i.e. Parkinson’s Disease), 3) there is a suspicion for delayed OhTN, 4) evaluating the risk for symptomatic OhTN in those with neurological pathology and dysautonomia, 5) considering the differential between an orthostatic and a vasovagal syncope, 6) the OhTN syncope cannot be differentiated from a psychogenic pseudosyncope. The procedure is carried out at a room temperature of 20-24°C with the patient lying down on a table to be inclined at 60-80°; at least every 3 minutes BP, heart rate and ECG tracing is carried out. Symptoms or syncope are considered to be a result of OhTN if they occur during testing in active or passive orthostatism, in parallel with a diagnostic drop in BP (at least 20 mmHg drop in SBP and/or 10 mmHg drop in DBP) and if they disappear in clinoostatism\textsuperscript{34}. A diagnostic drop in BP in the absence of recurring symptoms/syncope may allow the consideration of symptoms/syncope as being determined by OhTN\textsuperscript{1}. Tilt testing allows the differentiation between a hypotensive versus a vasovagal syncope. In the case of the latter, the BP drop during testing occurs rapidly (within a few minutes from test start) and is associated with relative bradycardia and...
prodromal symptoms (hot flush, diaphoresis, nausea). It is a useful test to select patients who might benefit from physical therapy, but is less relevant in monitoring therapeutic response in those with OhTN and neurologic pathology and dysautonomia.

Testing to evaluate for the etiology of OhTN include: 1) plasma NE levels, in elected cases, in the absence of specific neurologic manifestations, when there is a clinical suspicion for the occurrence of OhTN as a first sign of a synucleinopathy; the level of serum NE is diagnostic for neurogenic OhTN associated with PAF or PD when it does not double after 5-10 minutes of orthostatism; 2) plasma levels of vitamin B12, as there are data showing that B12 vitamin deficiency can associate OhTN; 3) laboratory testing for autoimmune diseases and serum levels of ganglionic acetylcholine receptor autoantibodies, to diagnose paraneoplastic syndromes, when there is a clinical suspicion for other causes of OhTN.

PROGNOSIS
Chronic OhTN has been associated with a poor prognosis. A meta-analysis on data available up to 2014 has shown that classical OhTN is an independent predictor for all-cause mortality. In the Malmö Project including 33,346 community patients aged over 45 years, all-cause mortality was 1.6 times higher in those with OhTN. Classical OhTN was associated with a higher rate of coronary heart disease, and in the case of the elderly with an increased risk for myocardial infarction. In the Malmö Project, acute coronary events significantly correlated with a decrease in DBP. Classical OhTN has been associated with a higher risk for atrial fibrillation, hospital admissions for heart failure, and an increased risk for non-lethal ischemic stroke and cognitive decline in those aged over 75 years. In the fragile elderly OhTN is a severe marker for deconditioning and presence of comorbidities carrying a severe prognosis. Even though OhTN is associated with a higher risk of falls, it does not equate to a similar risk for fractures. In those with synucleinopathies and delayed OhTN, 10 year mortality was 24%, and 56% after the OhTN associated the features of classical OhTN, with only a 6% mortality in the control group.

Initial OhTN, a risk factor for trauma from falls, does not appear to influence the risk of death.

OhTN secondary to reversible causes (dehydration, hemorrhagic anemia, excessive vasodilating or diuretic therapy, or the association of vasodilators with diuretics, alpha blockers, SGLT-2 inhibitors) resolves after the identification and correction of the trigger.

MANAGEMENT
The management of OhTN starts from the identification and avoidance/elimination of triggers, to non-pharmacological measures and pharmacological therapy.

Patient education is a major element to insure benefit in the management of OhTN. Patients should receive explicit but brief information on the underlying mechanism and general symptoms of OhTN, on the fact that it has no specific therapy that non-pharmacological measures are key elements in symptom control, and that pharmacotherapy is initiated only when non-pharmacological measures have failed to control symptoms and reduce the drop in BP with orthostatism.

NON-PHARMACOLOGIC MANAGEMENT
It includes avoiding assuming orthostatism abruptly, avoiding static orthostatism and prolonged bed rest. Particularly in patients with postprandial hTN it is recommended to avoid heavy meals with high carbohydrate content and alcohol consumption. One should associate measures to increase physical condition by exercise (counter pressure measures) which should increase isometric muscle tone predominantly in the lower limbs, favoring venous return and reducing symptoms of OhTN. The type of exercise should consider the age and physical status of patients, while the actual exercise should start with education on the topic and medical supervision. Valsalva maneuvers should be avoided as they can precipitate a syncope. Whenever possible, physical exercise carried out in pools (avoiding high temperatures) are preferred because they increase orthostatic tolerance as the pressure of the water against the body reduces the effect of the gravity on the sub-diaphragmatic venous vascular bed. Benefits of physical exercise have been reported in those with autonomic dystonia and vasovagal syncope.

Hypovolemia should be avoided by ensuring a daily oral water intake of 1500-2000 ml. In those with postprandial hTN an average 500 ml of water should be ingested before every meal. The salt intake will be recommended depending on the clinostatism BP level or the presence of heart failure. Administering 500 ml cold water reduces OhTN during the first 10-15 minutes from administration, most probably as a result of increasing NE plasma levels.
Sleeping with the head resting on a 30° inclined pillow (similar to tilt testing) sensitizes the carotid and aortic baroreceptors and those of the renin angiotensin aldosterone system and reduces morning OhTN53.

High waist elastic stockings reduce venous pooling by applying an external pressure in the lower limbs and become necessary for those with chronic venous insufficiency; orthostatic inflatable elastic abdominal supports reduce subdiaphragmatic venous pooling and are recommended particularly in patients with neurogenic OhTN54-56.

Identifying the drugs potentially triggering OhTN should be followed by dose reduction or even their avoidance. The decision should consider the risk benefit ratio – the risk for OhTN and their benefits for the condition for which they were indicated (diabetes, arterial hypertension, heart failure, chronic kidney disease, cancer, etc.). In patients with OhTN and clinostatism hypertension, the lack of BP control leads to cardiovascular events; maintaining a high clinostatism BP also increases glomerular filtration and diuresis, leading to the aggravation of OhTN. In this setting BP lowering therapy has to be supervised closely, as reaching the BP target in clinostatism will also improve OhTN symptom control. Even though there are little data from studies dedicated to the role of BP lowering medication in the development of OhTN, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium blockers are generally considered to be less associated with OhTN than alpha blockers, diuretics, and beta blockers1.

The correction of vitamin B12 deficiency (<250pg/mL)57 and the treatment of anemia by subcutaneous recombinant erythropoietin (50U/kg 2-3 times/week) in patients with primary autonomous dysfunction reduce the risk of an orthostatic BP drop, through mechanisms yet unknown58,59.

**PHARMACOLOGICAL THERAPY**

Pharmacological therapy is recommended when nonpharmacological measures have failed to control symptoms and reduce the drop in BP with orthostatism36.

The drugs used act either by increasing peripheral vascular resistance – midodrine, droxidropa and atomoxetine, or by increasing intravascular volume – fludrocortisone.

Drugs traditionally recommended for OhTN are midodrine and fludrocortisone, although their benefit to reduce OhTN is modest and limited by their adverse effects.

Midodrine acts as an alpha agonist through its metabolite desglymidodrine which leads to vasoconstriction and the reduction of orthostatic BP drop, but also the increase of BP in clinostatism. Its effects last for up to 3 to 4 hours and should be monitored in patients developing clinostatic hypertension 36 and heart failure. Its efficiency has been mostly studied in primary neurogenic OhTN60,61, to a much less extent in secondary neurogenic OhTN62. Midodrine is the first drug recommended in OhTN36. Its oral administration, titrated from 2.5 mg up to 15 mg, is given 3-4 hours before waking time, to avoid morning OhTN. An earlier administration would be ineffective and contribute to clinostatism hypertension. A clinostatism SBP over 180 mmHg is a contraindication for midodrine. Secondary effects include headache, urine retention, piloerection51,61.

Fludrocortisone, a synthetic mineralocorticoid, reduces OhTN mainly by volume expansion secondary to water and salt retention, but also through an increase of NE and angiotensin II pressor effect, which contributes to the acceleration of target organ damage such as left ventricle hypertrophy and chronic kidney disease63. The volume expansion may lead to an increase in clinostatic BP, an effect more pronounced when associated with midodrine. Its addition to midodrine is warranted only by the lack of symptom control with the latter. On the long term, adverse effects of fludrocortisone include hypokalemia and hypercorticism. It should be avoided in those with heart failure64.

Drugs recently tested to correct OhTN dysautonomia are doxidropa and atomoxetine.

Droxidropa is a synthetic aminoacid converted in NE by the enzymatic intervention of an aminoacid decarboxylase available in the nervous tissue and other tissues. Its mechanism of action appears to be related to the increase in NE synthesis and release in the sympathetic nervous fibers from the neuro-vascular space, but also to the increase in NE synthesis in the extraneural space51. Droxidropa was proved effective in reducing neurogenic OhTN65, and was approved by the FDA for treatment of OhTN in PD, MSA, PAF and non-diabetic peripheral autonomous neuropathies, as a result of clinical studies and a meta-analysis published in 201666. The 2017 ACC/AHA/HRS Guidelines for the management of syncope recommends doxidropa with a IIIa level of indication to treat orthostatic syncope67. Its administration is recommended depending on the 24h profile of OhTN, and is titrated from 100 mg to 600 mg, 3 times daily13. In 30% of patients there is
no clinical improvement. In those with neurogenic OhTN, the low NE level in clinostatism (<220 pg/mL) predicts the clinical response to doxidropa. The ESC 2018 Guidelines on syncope comment on the lack of data to support its efficacy on long term use which would require more clinical trials.

Atomoxetine acts by blocking NE reuptake in the postganglionic sympathetic synapses as a result of its binding to the NE cotransporter. The mechanism of action explains the pressor effect of atomoxetine in patients with MSA, where peripheral neurons are unaffected, its limited effects in patients with PAF, where these neurons are primarily affected, or in those with PD and LBD, where the autonomous peripheral system is affected during the course of disease. The NE plasma levels predict the response to atomoxetine. It may be associated with droxidopa, with careful monitoring and attention to the potential arrhythmic effects of their co-administration. The association between atomoxetine and pyridostigmine, which increases nicotinic neurotransmission in the sympathetic ganglia by inhibiting acetylcholinesterase, has additive effects and improves orthostatic tolerance in those with severe sympathetic autonomous dysfunction.

In specific situations, OhTN therapy may include:
- Desmopressin indicated in patients with morning OhTN after excessive nocturnal diuresis, however with little clinical benefit in studies.
- Acarbose and octreotide are indicated in those with postprandial hTN. Oral acarbose reduces glucose absorption and postprandial insulin levels, influencing postprandial hTN through its vasodilating effect. Octreotide reduces postprandial hTN by reducing the release of vasodilating intestinal peptides, however with limited indications due to the subcutaneous administration and adverse effects (abdominal pain and diarrhea).

CONCLUSIONS
Orthostatic hypotension is a cardiovascular anomaly frequently found in clinical conditions that either primarily or secondarily affect the central and/or peripheral autonomous nervous system. It is associated with poor outcomes. Further research is mandated to confirm the relationship between OhTN and cardiovascular morbidity and mortality, and to assess whether it is indeed a marker of cardiovascular disease severity or a risk factor for the development of major cardiovascular events. The efficacy of currently available drug therapy is limited, having a modest effect on quality of life, at the expense of lack of evidence of prognostic significance.

Conflict of interest: none declared.

References
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