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Review article

Peripheral arterial disease: A growing problem for the internist

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Abstract

The atherothrombotic conditions, coronary artery disease, cerebrovascular disease and peripheral arterial disease (PAD), together account for almost one-half of all deaths in Europe each year; however, perception of the specific risks associated with PAD is generally poor compared with its related conditions. PAD is not just a localised disease — it has serious systemic effects, and affected individuals have a higher risk of serious cardiovascular sequelae or death within 1 year of diagnosis compared with those with coronary artery or cerebrovascular disease. PAD, which currently affects approximately 16% of the general population aged over 55 years, is increasing because of the population aging and the continuing rise in cardiovascular risk factors. The management of PAD is a multi-disciplinary approach, and while this can have its advantages, it can also mean that responsibility for patient care is unclear. Globally, almost one-third of all patients with PAD are under internist care. Internists are ideally placed to identify patients at risk of PAD and initiate prompt risk factor management because of their role in the continued care of elderly patients and those with diabetes, hypertension, dyslipidaemia, and chronic renal disease. Multi-disciplinary guidelines for the clinical management of PAD, based on consensus among international specialists in a number of fields, have been developed to create an informed, unified and proactive approach to the treatment of PAD. They stress the continuity of care, the use of office-based ankle–brachial index testing to aid early diagnosis, and prompt and aggressive risk factor management.

Keywords: Peripheral arterial diseases; Intermittent claudication; Risk factors; Aged; Ankle–brachial index; Polyvascular disease

1. Introduction

Coronary artery disease (CAD) and cerebrovascular disease (CVD), together with peripheral arterial disease (PAD), are responsible for the deaths of more adults than any other medical condition [1]. The trio arises from a common aetiology and are differing manifestations of atherothrombotic disease occurring in the vascular beds of the heart, brain and lower limbs respectively.

Each year in the European Union, cardiovascular diseases cause more than 1.9 million deaths (accounting for 42% of all mortality), and in Europe as a whole the mortality rate is even higher at about 49% (more than 4.35 million deaths per year) [2]. All three conditions have serious implications for the life and health of affected individuals, but of the trio, it is the impact of PAD that is most often underestimated, by physicians as well as patients [3].

2. Consequences of peripheral arterial disease

PAD is a major cause of acute and chronic illness. It is associated with disability and a reduced quality of life.

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However, in addition to problems of mobility, the systemic nature of the atherothrombotic process also contributes to an elevated risk of further cardiovascular sequelae.

Individuals with PAD face an increased risk of cardiovascular ischaemic events (Fig. 1) [4]. The international REduction of Atherothrombosis for Continued Health (REACH) registry consisting of more than 68,000 patients found that individuals with documented PAD had higher 1-year cardiovascular event rates (including cardiovascular death, myocardial infarction [MI], stroke or hospitalisation for atherothrombotic events) than patients with CAD or CVD [4]. This has also been demonstrated by Hackam et al in a Canadian registry study where patients affected by PAD incurred an increased risk of adverse cardiovascular events, including stroke, MI and vascular mortality [5]. Outpatients with PAD taken from two national, prospective, practice-based registries of 9810 patients with vascular disease, diabetes mellitus or aged over 65 years with at least two additional cardiovascular risk factors, had a nearly two-fold higher risk of major cardiovascular events at 6 months than patients without PAD (7.3% vs. 4.1%; $p<0.0001$). Hackam et al found that approximately 1 in 8 patients with PAD experienced a vascular event or required hospitalisation for cardiovascular-related events during the following 6 months — a rate considerably higher than patients without PAD. In Italy, a study in general practice reported an associated four-fold increase in overall mortality and a nearly eight-fold increased risk of cardiovascular-related death in patients with PAD [6].

Co-existence of cardiovascular diseases is common due to the generalised nature of atherothrombotic disease. Concomitant coronary heart disease has been detected in approximately 90% of patients with PAD undergoing coronary angiography, and concomitant CVD in approximately 50% of patients with PAD tested [7,8]. Patients with more than one co-existing

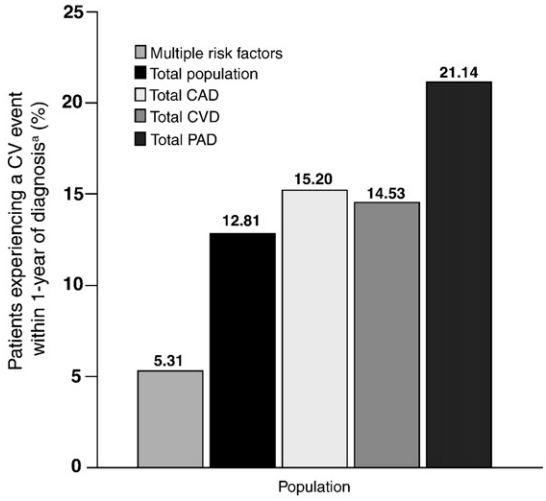

Fig. 1. PAD is a major cause of cardiovascular events and death within 1 year of diagnosis (REACH, REduction of Atherothrombosis for Continued Health study [$n=68,236$]) (adapted from Steg et al [4]). CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; and TIA, transient ischaemic attack, [a]Adjusted for age and gender. [b]CV death, MI, stroke or hospitalisation for atherothrombotic event (including TIA, unstable angina or worsening of PAD).

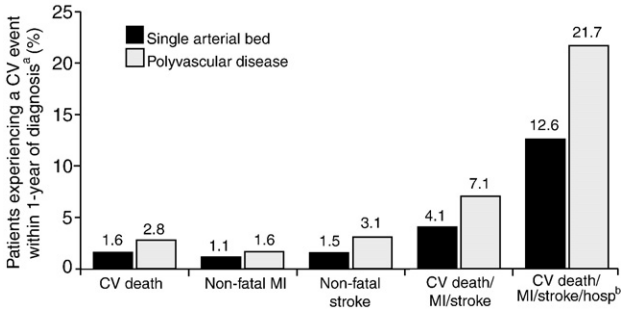

Fig. 2. Patients with polyvascular disease have poorer outcomes (REACH, REduction of Atherothrombosis for Continued Health study [$n=68,236$]) (adapted from Steg et al [4]). CV, cardiovascular; MI, myocardial infarction; PAD, peripheral arterial disease; and TIA, transient ischaemic attack, [a]Adjusted for age and gender. [b]Hospitalisation for atherothrombotic event such as TIA, unstable angina, worsening of PAD.

cardiovascular condition (polyvascular disease) have almost double the risk of cardiovascular-related events, hospitalisation or death compared with those with disease in one vascular bed only (Fig. 2) [4]. Such patients face a high risk (>10%) of a major cardiovascular event within 1 year of diagnosis [4].

3. Peripheral arterial disease is a growing concern

More than 27 million people across Europe and North America are thought to be affected by PAD, equating to 16% of the population aged over 55 years [9]. There is concern that this number could increase through the combination of aging of the population and the continuing rise in cardiovascular risk factors such as diabetes and obesity [6,10,11]. Currently, the overall prevalence of PAD appears to be constant despite improvements in treatment strategies and medical understanding, and the introduction of successful risk factor modification programmes (including smoking cessation programmes) in some areas [1,12].

Of the individuals affected by PAD in Europe and North America, an estimated 10.5 million are symptomatic while approximately 16.5 million are asymptomatic [9]. The prevalence of asymptomatic PAD has been estimated to be as high as 20% in the total adult population, rising still further in some at-risk populations.

4. Peripheral arterial disease is underdiagnosed and undertreated

Despite the widespread effects on the population, physician awareness of PAD is surprisingly low; far lower than that of MI and ischaemic stroke, and the condition is not widely recognised. In one study, only 49% of physicians were aware that their patients had previously received a diagnosis of PAD, compared with 83% of the patients [3].

Research shows that less than 25% of patients with PAD are undergoing treatment and that undertreatment with established therapies (such as antiplatelet agents and statins) is common [13]. In a study of more than 50,000 patients, Cacoub et al showed that atherothrombotic risk factors were less likely to be

controlled in patients with PAD than patients with a diagnosis of CVD or CAD. Approximately 46% of patients with PAD had no risk factor control and only 28% had full risk factor control according to recognised guidelines [14]. However, when patients with PAD also had co-existing CAD, the number of patients with all risk factors controlled rose to more than 50%.

One explanation for the lack of an aggressive approach could be that the long-term consequences of PAD are generally underestimated by the medical profession [3,15,16]. In the ATTEST study, French physicians were asked to predict future outcomes for patients with PAD, CAD or ischaemic stroke. In general, physicians underestimated cardiovascular risk for patients with PAD whereas the amputation risk for such patients was greatly overestimated; only 27% predicted a 5-year cardiovascular risk of >20%, whereas 44% predicted <5% risk of limb or digit amputation within 5 years corresponding with published data reporting a 2% risk at 5 years [16].

5. Understanding the risk factors for peripheral arterial disease

The epidemiology and clinical consequences of PAD are closely associated with classic atherothrombotic risk factors (Fig. 3); of these, those most associated with a poor prognosis in PAD are previous or current smoking, diabetes, and those aged over 65 years. PAD incidence increases with age, and studies across Europe have demonstrated high levels of PAD in the elderly population. In Sweden, almost one-fifth of individuals aged over 65 years have some stage of the disease [12]. Research has also shown that PAD prevalence is similar between men and women, confounding current expectations. Sigvant et al have suggested that women might be more likely to be affected by the asymptomatic form of the condition [12].

6. The role of the internist in the management of peripheral arterial disease

There have been public calls for more healthcare professionals to become involved in reducing the impact of PAD whenever and wherever it is detected [5,9] reflecting the broad nature of the condition and the patient numbers involved.

Internists, who are intimately involved in the care for elderly patients and those with risk factors for PAD (including diabetes, hypertension, dyslipidaemia or chronic renal disease), are ideally placed to identify patients at risk of PAD and initiate risk factor management. The international REACH study showed that almost 30% of patients with PAD worldwide are currently under internist care, with family practitioners being the only group of healthcare providers who have responsibility for more patients with PAD [17].

The early detection of PAD – particularly asymptomatic or atypical disease – in patients known to be at risk and the prompt instigation of appropriate risk reduction strategies can have a major impact on patient outcomes. In fact, the German epidemiological study on ankle–brachial index (getABI), an observational study of patients aged over 65 years screened for

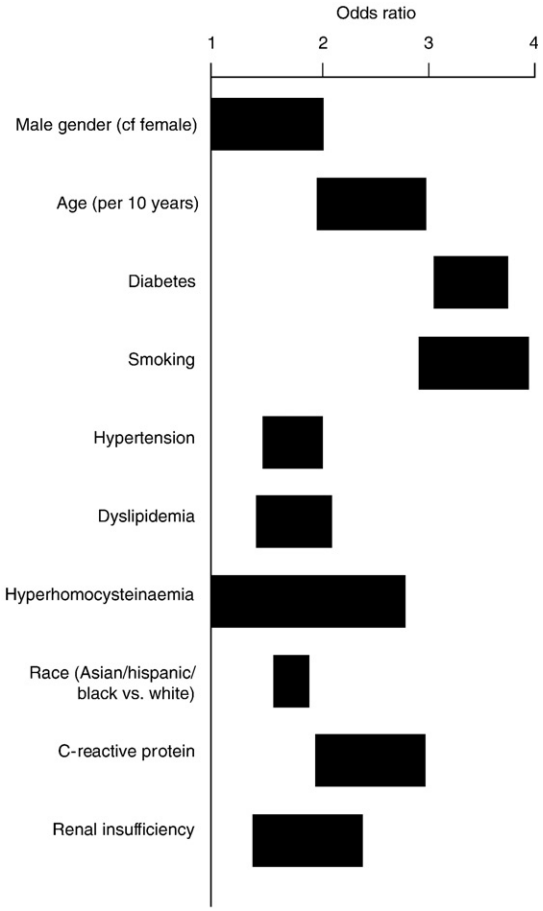

Fig. 3. Risk factors for PAD [19]. Reprinted from Eur J Vasc Endovasc Surg, 33, Norgren L Hiatt WR (eds) Inter-Society Consensus for the management of Peripheral Arterial Disease (TASC II), S1–S75, Copyright 2007, with permission from Elsevier.

PAD in primary care, found that patients with asymptomatic PAD are at an equally high risk of 5-year mortality as patients with symptomatic PAD, and at twice the risk of patients without PAD [18].

7. A multi-disciplinary approach to management

The importance of a multi-disciplinary approach is reflected in recent international guidelines, which have drawn upon the expertise and knowledge of a variety of professional societies to develop an informed and unified approach to the treatment of PAD. The inter-society consensus for the management of peripheral arterial disease (Trans-Atlantic Inter-Society Consensus II [TASC II]) guidelines for the clinical management of PAD are based on consensus among international specialists in a number of fields — vascular surgeons, interventional radiologists, angiologists, vascular medicine physicians, cardiologists, diabetologists and podiatrists [19]. TASC II aims to unify the approach to PAD management and to increase awareness of the need to proactively manage PAD among many different groups of healthcare professionals, including primary care physicians and internists.

The TASC II guidelines provide up-to-date, evidence-based recommendations for the diagnosis and clinical management of

all aspects of PAD and associated risk factors, and are an invaluable resource, although some adjustment might be needed to take local situations into account. According to its editors, TASC II exists largely to emphasise the close relationship between PAD and CVD, which is the reason for the highly increased mortality of patients with PAD, and to stress the need for prompt modification of risk factors [20]. Additionally it provides guidelines for the appropriate referral to vascular specialists, so that the opportunity to save a leg is not lost. TASC II is organised to follow an anticipated 'chronology' of the clinical care of patients with PAD so that the pathway of care and appropriate referral points are clearly signposted.

8. Awareness of peripheral arterial disease needs improving

Prompt treatment of vascular disease can diminish disability and death. Early diagnosis of PAD can be difficult as it is not instinctive for patients to associate the symptoms with underlying arterial disease (for example, the classical signs of claudication that disappear at rest). It is necessary to be proactive in asking about PAD because most patients have a low awareness of the condition and of the seriousness of its consequences, and might not consider their symptoms important or relevant enough to raise at the consultation.

Most patients do not know the signs and symptoms of PAD; the language used to describe them can be vague (fatigue, aching, numbness etc) and the primary site(s) of discomfort can vary — from the buttock, to the thigh, foot, or classically in the calf, with symptoms being present either at rest or on exertion. It is also easy for symptoms to be dismissed as muscular or joint pain, or as part of the general aging process.

Hirsch et al have found the public to be poorly informed about PAD in general, even in individuals with prior experience of cardiovascular events (for example, a transient ischaemic attack or angina) [21]. Public awareness of PAD lagged behind those of other commonly seen conditions, with only approximately 26% of the individuals surveyed (all of whom were aged 50 years or over) being aware of PAD, compared with 67% for MI and congestive heart failure, and 74% for stroke. Even amongst those who claimed to know about PAD, knowledge was poor, with 50% not aware that diabetes and smoking were risk factors for PAD and 25% unaware of the increased risk of other cardiovascular conditions.

9. The importance of early detection of peripheral arterial disease

PAD can be difficult to detect if patients do not present with classical limb symptoms. The signs and symptoms of PAD can be atypical and easily missed or masked through a lack of physical activity [22,23]. Intermittent claudication has long been considered the classical marker of PAD, yet Diehm et al have shown that an over-reliance on the classical symptoms of intermittent claudication will markedly underestimate the prevalence of the condition [10]. Only 10% of patients aged over 65 years diagnosed with PAD by their family practitioner will have had intermittent claudication [10]. In addition, intermittent claudication cannot be taken as a sole measure of function impairment [22].

There is a wide range of leg symptoms and functionality in patients with PAD. Typical signs and symptoms of PAD include intermittent claudication (pain in the leg, commonly localised to the calf muscles, which appears when walking and disappears when at rest). Less frequently seen signs and symptoms of PAD are numbness; weakness or heaviness of the leg; aching or pain in the feet and toes when at rest; cold legs or feet (especially if there is a marked difference between the legs); hair loss or change of skin colour on the legs and slow healing sores. A full patient assessment should always include a history, clinical examination (pulse palpation) and objective testing using ankle–brachial index (ABI) measurement.

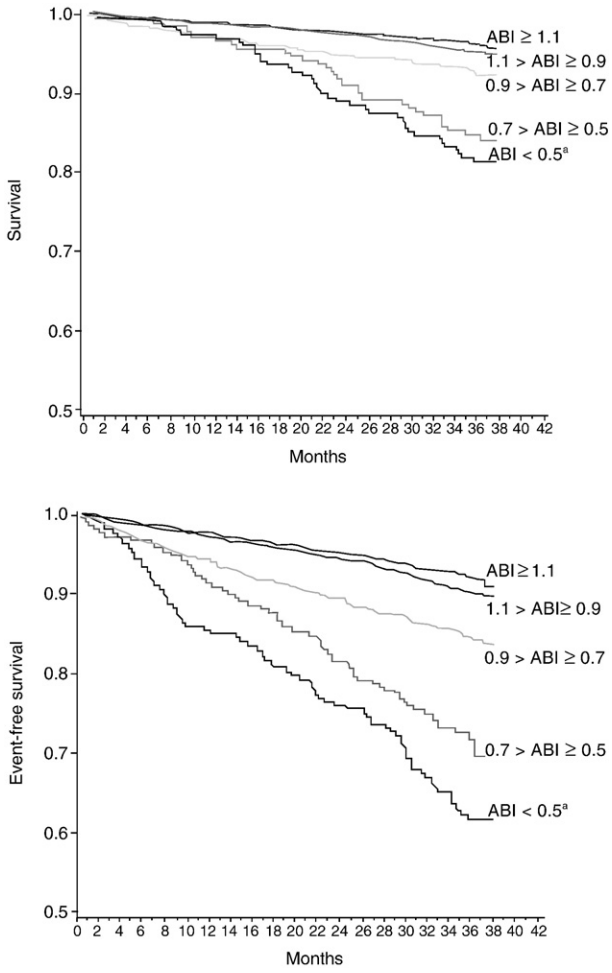

Fig. 4. Patient outcomes worsen with lower ABI scores (taken with permission from Diehm C, et al. Association of low ankle–brachial index with high mortality in primary care. Eur Heart J 2006;27:1743–9) [23]. Figure shows survival (top) and event-free survival (bottom) according to ABI category over 3 years. Kaplan–Meier estimates of total survival (top) or event-free survival (i.e. no severe vascular events) in the five pre-defined ABI categories during the follow-up period. ABI, ankle–brachial index. [a]ABI<0.5 or history of peripheral revascularisation or amputation at baseline.

10. Ankle–brachial index — a key tool in the diagnosis of peripheral arterial disease

ABI is a quick, simple and accurate non-invasive test for PAD that can be performed in an office environment by a trained physician or nurse. It is easy to teach and to learn and has a high degree of reproducibility and reliability [24]. Research has shown that patient outcomes are associated with lower ABI values, both in terms of patient mortality and the likelihood of future cardiovascular events (Fig. 4) [23]. An ABI value of <0.9 is usually taken as a pathological indicator of PAD and has a high level of specificity as a predictive marker of future cardiovascular events (Fig. 5) [23,25,26]. It is recognised as a valuable tool in the detection and management of PAD by many clinicians [27,28]. Yet despite these advantages, ABI testing is still underutilised. One recent French study showed that only a third of patients with PAD had received an ABI test [16].

ABI testing has a varied role. It is a key tool with which to identify individuals with asymptomatic PAD, some of whom might have had symptoms masked through a lack of general mobility. It can also provide valuable additional information to confirm a diagnosis or to provide more details for risk stratification and long-term outcomes. However, in patients with intermittent claudication, a normal ABI cannot exclude the condition and in patients with diabetes or chronic renal failure, normal or high ABI values can sometimes be misleading because of excessive vascular calcification. In such patients further tests are recommended, for example the measurement of pedal pulses, or if this is not possible, toe systolic pressures, pulse volume recordings or duplex ultrasound imaging [19].

ABI is also used as an extra level of risk assessment for borderline cases of pharmaceutical management. In a study of more than 48,000 healthy patients, the addition of an ABI score substantially improved the prediction of mortality determined by Framingham risk score. The inclusion of an ABI score to their total risk stratification was found to increase risk in almost 10% of the individuals measured [26].

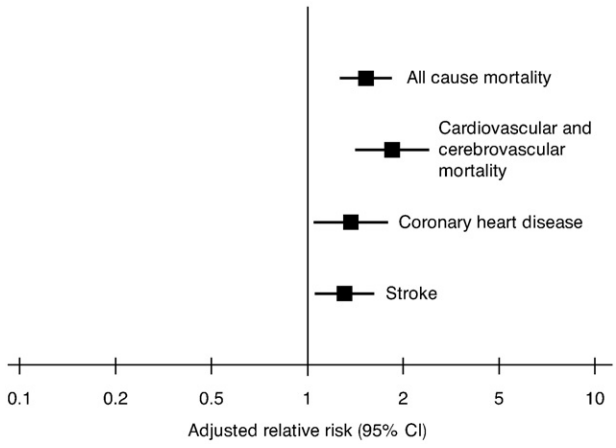

Fig. 5. An ankle–brachial index of <0.9 is associated with an increased risk of cardiovascular events and mortality — pooled analysis from 11 studies (n=44,590) (adapted from Heald et al [26]) CI, confidence interval.

Table 1
Effects of pharmacological risk factor modification for peripheral arterial disease on all-cause mortality (n=2420 with ankle–brachial index <0.9; Median follow-up: 8 years.

Drug treatment	[a]Hazard ratio (95% confidence interval)
Statins	0.46 (0.36–0.58)
Beta-blockers	0.68 (0.58–0.80)
Anti-platelets	0.72 (0.61–0.84)
ACE inhibitors	0.80 (0.69–0.94)

ACE, angiotensin-converting enzyme.
1067 patients (44%) died) (adapted from Feringa et al. [[29]*]).
[a] Adjusted for risk factors and propensity scores.

TASC II calls for the adoption of ABI testing to provide a clear objective means of identification of asymptomatic and symptomatic PAD. The guidelines recommend that an ABI should be measured in patients who: have leg symptoms on exertion; are aged 50–69 years and have a cardiovascular risk factor (particularly diabetes or smoking); or are aged 70 years or older, irrespective of risk factor status. In addition, where risk tables are employed (for example, Framingham or SCORE), TASC II recommends ABI testing in patients who have a Framingham risk score of 10–20%.

11. Clinical management of individuals with peripheral arterial disease

The clinical management of patients with PAD involves the modification of as many risk factors as possible by a combination of lifestyle management and, if necessary, by pharmacological intervention. Risk factors can be modified independently or as part of an overall total risk reduction strategy. Patients with a cardiovascular high risk (for example, because of multiple risk factors or polyvascular disease) should be treated more aggressively, according to the target goals laid out in TASC II [19].

Smoking cessation and weight reduction programmes, with appropriate counselling if necessary, have proved effective and are the mainstay of lifestyle management. Pharmacological risk factor modification involving statins, antiplatelet agents (such as aspirin or clopidogrel) and antihypertensive agents have proven beneficial in symptomatic patients (Table 1) [28]. For patients with the symptoms of claudication, cardiovascular risk factor reduction alone will typically not provide relief from pain or discomfort. For these patients, exercise therapy remains the primary mode of treatment.

12. Conclusions

Increased awareness of the cardiovascular risks associated with PAD and adoption of up-to-date evidence-based guidelines, such as TASC II, by all healthcare professionals who come into contact with patients at risk for PAD could substantially help in improving patient prognosis [19]. Internists are ideally placed to help in this effort because of their continued proximity to groups of high-risk patients, such as those with diabetes or renal disease.

Learning points

- PAD affects approximately 16% of the general population aged over 55 years in Europe and North America and is on the increase.
- Almost one-third of all patients with PAD around the world are under internist care.
- PAD is not just a localised disease — it also has serious systemic effects and is a major cause of death and disability.
- Individuals with PAD have higher risk of serious cardiovascular events within 1 year of diagnosis than those with CAD or CVD — yet physicians and patients are less aware of the risks associated with PAD than of those of MI or ischaemic stroke.
- More than 20% of individuals with PAD in the general population do not show classical symptoms and are diagnosed through ABI measurement alone — the proportion is much higher in at-risk populations.
- ABI is a quick, simple and accurate non-invasive test for PAD that can be performed in an office environment by any trained physician or nurse.
- Early diagnosis and prompt risk factor management to established guidelines can greatly diminish PAD-related disability and death.

Disclosure of interest statement

Denis Clement has received honoraria for speaking engagements and as a scientific advisor from all major pharmaceutical companies. Christopher Davidson has received honoraria from pharmaceutical companies for speaking engagements, and as a chairman for B-MS sponsored meetings. Curt Diehm has received an unrestricted grant from sanofi-aventis, Berlin, for the German getABI study. Jan Willem Elte has received honoraria for acting in an advisory role for MSD and GSK, and from MSD, sanofi-aventis, GSK, Novo Nordisk and Lilly for speaker engagements. Daniel Sereni has received honoraria from B-MS as a speaker. Coen Stehouwer and Marc Lambert have declared no conflicts of interest.

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