1 Epidemiology of PAD and CLI: a global and national perspective

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The global burden of peripheral artery disease (PAD) increased dramatically during the past decades and is predicted to further arise. Despite still being underrecognized, PAD is nowadays estimated to affect over 200 million patients worldwide.[1]

The rapid progress of PAD occurs in countries worldwide throughout all developmental stages (Figure 1.1).

The global spreading of the disease is affected by a variety of environmental and socioeconomic factors such as ethnicity, income, or gender. Ethnic groups that were shown to be associated with increased prevalence of PAD are African-American (8.8% at age >40 years), and native American (6.1%) compared to non-Hispanic caucasian (5.5%), whereas Hispanic (2.8%) and Asian ethnicity (2.6%) had lowest PAD prevalence.[2] Hereditary and genetic conditions are under current investigation as they are suspected to modestly promote the individual risk of

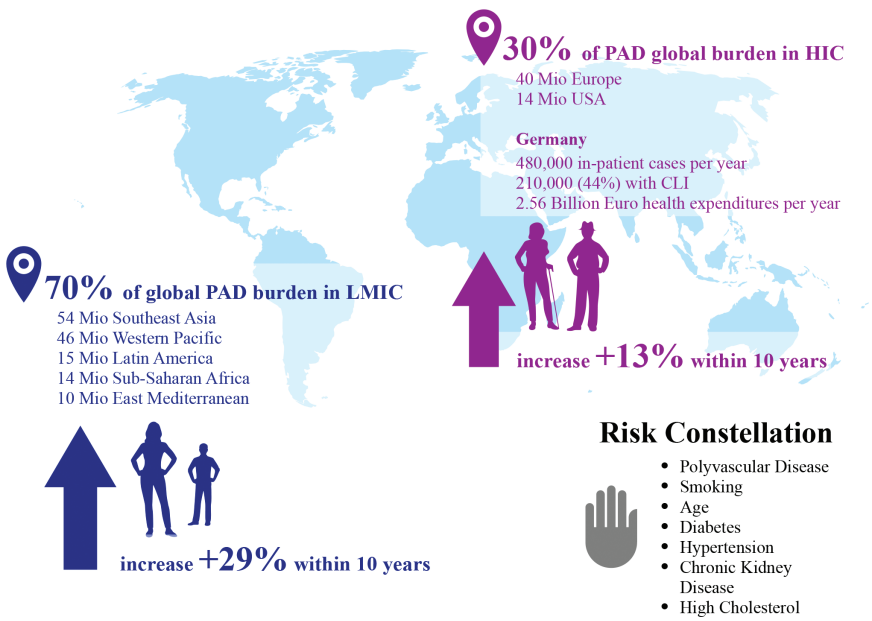

FIGURE 1.1 Peripheral artery disease: epidemiology at a glance.

disease. However, according to current opinion hereditary might not significantly impact on the recently observed trends of global or regional PAD burden.

Economic globalization involves fundamental changes in (supra-)regional health care markets. These developments inseparably accompany and impact on the epidemiological trends in PAD transition. Financial wealth is strongly associated with the risk of arteriosclerotic diseases in a population, and further regulates health care supply for patients. About 70% of people globally affected with PAD live in low- and middle-income countries (LMIC).[3] The prevalence of PAD in these areas increased clearly above average by about +29% within only one decade (2000-2010). Global estimates show highest PAD prevalence particularly in Southeast Asia (54.8 million) and Western Pacific regions (45.9 million), followed by Latin America (15.5 million), sub-Saharan Africa (14.2 million), and the eastern Mediterranean (10.3 million). Studies on urban Malaysian patients show a high prevalence of PAD being detected in 23% of patients at high cardiovascular risk. It is well illustrated that in these countries PAD is still highly under-diagnosed, since all diagnosed for the first time within the framework of the study.[4] Despite the prevalence of PAD in LMIC is highest in the middle age groups (35-65 years), a disproportionate increase of PAD of more than +40% per ten years could be observed particularly in higher age groups >75 years. In contrast to countries of higher income, PAD prevalence in LMIC is reportedly higher in women, notably in females at younger ages. Thus, female populations suffer of PAD in 6.3% *versus* 2.9% males (relative difference +217%) at the age 45-49 years, and numbers rise up to 12.3% *versus* 10.1% (+122%) at the age 75-79 years.[1] Notably, many of these patients in LMIC are (yet) at asymptomatic stages of disease. These trends in LMIC are likely to be driven by socioeconomic and environmental factors that add to the worldwide increasing traditional risk factors and demographic ageing of populations.

In High-Income Countries (HIC), PAD affects over 40.5 million people in Europe, and more than 14.3 million US citizen.[1] Its spreading has increased in the recent past by approximately +13% per decade (2000-2010). Given an average prevalence of 5.3% in the general population of the European continent countries, PAD prevalence is higher as compared to the European Union (3.4%), and in particular strongly developed in Greece (28%), Italy (23%), UK (20%), and Sweden (18%) (prevalences refer to age groups >60 years).[5] PAD prevalence ranges with strong dependence on age between 5% at 45-49 years up to 18% in 85-89 years in the overall population. In HIC, the incidence of symptomatic PAD comprising intermittent claudication, pain at rest, or ischemic ulcer is reportedly higher than in LMIC. Likewise, the incidence of intermittent claudication is strongly age dependent and varies between the developed countries from comparably low levels of 0.2% (Iceland) up to 1% (Israel) in a population aged approximately 60 years.[6] In Germany, every year over 480,000 in-patient cases (corresponding to 2.67% of an annual 15 million hospitalisations nationwide) are registered due to PAD and therewith related complications (2009).[7] During hospitalisation, approximately 94,700 endovascular revascularizations, 38,000 peripheral bypasses, 16,700 major, and 24,700 minor amputations are conducted every year. Applying to 44% in advanced stages of disease with critical malperfusion, the treatment of PAD amount to a total annual financial burden of about 2.56 million Euro in the in-hospital sector. These data point out the utmost importance of early prevention of PAD onset and progression to critical stages.

Critical limb ischemia (CLI) as the most severe condition of PAD at its late clinical stages is characterized by critical malperfusion of the lower limbs. Clinical symptoms comprise typically limb pain at rest, as well as the presence of ischemic peripheral ulcer or gangrene. However, clinical presentation may be atypical by reason of concomitant nerval or functional impairment, differences in symptom perception or overlapping pathologies such as infection, edema or diabetic foot syndrome. These may not only alter clinical appearance but also limit application and validity of objective diagnostic testing such as arterial pressure or peripheral oxygen saturation. Therefore the assessment of

the definite incidence of CLI and its clinical course can be challenging to a certain extent. In the U.S., an annual incidence of 0.35% of CLI in the general population >40 years, corresponding to a prevalence of 2.35% has been reported according to health claims data (2003-2008).[8] In the European countries, CLI prevalence has been estimated to about 1.2% in a Swedish general population aged 60-90 years. British data refer annual incidences of CLI with 220 cases per million population (0.022%).[9] In Germany, CLI leads to approximately 210.000 hospitalizations per year, corresponding to 44% of all in-hospital cases for PAD.[7] This CLI subset is being characterized as approximately 3-5 years older, and the ratio of female patients is with approximately 40% higher compared to that of lower PAD stages. Further, CLI cohorts are characterized by higher rates of traditional cardiovascular risk factors and multi-morbidity including polyvascular disease.

Against the background of worldwide ageing populations, a further increase of PAD and particularly its advanced clinical stages is expected in the near future. With an estimated life-span of currently 79 years for male and 84 years for female citizen in Germany, the epidemiological development of PAD already puts the health-care system at a big challenge. Life expectancy not only affects PAD onset and progression to critical stages, but also its treatment and prognosis on multiple levels. With increased age, there is a high chance of previous multiple endovascular and/ or surgical treatments performed at the side of the affected limb, that often involve complex procedures. In addition, patients at higher age often present at multimorbid physical status, including life-affecting physical states such as stroke, myocardial infarction, or chronic hemodialysis. Therewith involved, the rate of prescribed drugs in this patient clientele, including anticoagulants, puts them at increased risk for potential interactions, complications and adverse outcomes. The senescence of PAD patients in particular with high frailty involves further challenges on their potential for rehabilitating. The benefits and risks in elderly populations cannot be reliably numeralized since this high-risk patient clientele is largely excluded from systematic analyses on a big scale. The few existing data on elderly PAD cohorts indicate senescence driven factors such as functional dependence or increased frailty to be associated with impaired outcome after invasive procedures rather than the high age alone.[10] In summary, this growing high-aged patient clientele sets high demands on health-services structures and supply in the near future.

Females with arteriosclerotic manifestations are at average 4-6 years older than men. Formerly being regarded as a disease predominantly affecting males, the standpoint on PAD distribution between the sexes has relevantly changed in the recent past. In industrialised nations, PAD prevalence per Ankle-Brachial Index (ABI) definition, including mild and asymptomatic stages is now reported to be about equally distributed in men and women.[1] Apart from any gender issues and changed lifestyle behavior in female populations, these trends have been suggested to notably reflect improved detection of low-stage PAD in women as a consequence of the standardized use of the ABI method. The high validity of technical diagnostic tools such as ABI (sensitivity 80-95%, specificity 95-100%) and ultrasound duplex sonography now hold the opportunity of early onset of secondary preventive measures independent from physician's personal bias. However, women report significantly less often clinical symptoms such as intermittent claudication compared to male patients. Thus, the overall incidence of intermittent claudication is almost twice as high in men compared to women, and does not align until the age of 65 years.[6] Whereas some studies indicate lesser symptom presentation in female patients despite equal malperfusion indices, others report higher percentage of borderline malperfusion indices in women (ABI 0.90-0.99; 10.6% in women *vs.* 4.3% in males; Multi-Ethnic Study of Atherosclerosis). The longer symptom free periods in women may contribute to delayed diagnosis and treatment initiation in female PAD patients. This further may explain their later contact with the health-care system in the clinical course, but then their presentation at more severe clinical stages.

In Germany, 35% of all in-patient treatments for PAD apply to women. With

increasing stage of PAD, the percentage of females increases and reaches almost 40% in critical limb ischemia (Rutherford 4-6).[7] In topical debates, the role of sex is being highly investigated in matters of inappropriate or insufficient treatment supply in symptomatic PAD. Recent large-scaled data on unselected PAD patients in a real-life scenario show about equal revascularization rates in the in-hospital (65%) and a 4-year follow-up period (71%) for male and female PAD patients.[11] Against the background of a general under-treatment in end-stage PAD, revascularization rates in patients with ischemic ulcer or gangrene add up to not even 50% with no significant differences with respect to patient's sex. However, surgical approach is somewhat more common in male PAD patients (26.1% *vs.* 24.5%), whereas endovascular revascularization is slightly more often applied to female patients (42.8% *vs.* 47.4%). Male patients are commonly reported to have higher burden of traditional cardiovascular risk factors, however in-hospital mortality rates between male and female patients are reported about equal at 3% risk. Nevertheless, male sex has been shown to be associated with higher in-hospital amputation (11% *vs.* 9%) and significantly increased risk of long-term amputation (HR 1.284) and death (HR 1.155).[11]

Apart from demographic changes, personal health behaviour affecting individual cardiovascular risk is subject to continuous changes in men and women of all ages. Traditional risk factors, such as smoking (Odds ratio 2.1), diabetes mellitus (OR 1.7), or hypertension (OR 1.4) promote the progressive global burden of PAD in populations of both, LMIC and HIC.[1]

In Germany, hypertension is highly co-prevalent to PAD in 68% of all in-hospital treated cases, followed by diabetes (35%), chronic kidney disease (29%), or chronic heart failure (15%) (2009).[7] Particularly patients with critical limb ischemia (CLI) frequently present with multimorbid health status, thereof concomitant diabetes being prominently prevalent in one-in-two patients with ischemic tissue loss.

Diabetes mellitus is one major risk factor for the development of arteriosclerosis and lower limb PAD. Its enormously high global prevalence with currently 382 million people (2013) is further predicted to rise up to 592 million people worldwide.[12] The concomittant presence of diabetes mellitus promotes the development of polyvascular disease (30% in elderly PAD patients >65 years in a primary care setting.[13] Every 1% increase in haemoglobin A1c levels increases the risk of PAD by 26%.[14] Diabetes is evident in 23% of claudicants, 26% of PAD patients with ischemic rest pain, and in 44-49% of patients with ischemic ulcer/ gangrene.[15] Also, the duration and extent of hyperglycemia are highly predictive factors for PAD onset and progression to CLI. Diabetes particularly leads to highly calcified media sclerosis that predominantly affects the infrainguinal arteries (below-the-knee BTK-PAD). Analyses on smaller cohorts show that 24% of CLI patients have non-compressible Ankle-Brachial-Indices (ABI) indicating severe calcification.[16] BTK- and small artery PAD have been shown to be present in about 38% of CLI patients[17] and therefore to be strongly and independently associated with ischemic ulcer (OR 13.25, 95%-CI 1.69-104.16).[18] BTK-PAD in diabetic patients is often further complicated by the multifaceted effects of diabetic metabolism on peripheral nerves, wound healing and immune status. These conditions often involve restricted application of revascularization procedures in these patients although highly indicated (revascularization in Rutherford 6: 46.5% in patients with diabetes *vs.* 51.8% in patients without; $P<0.001$).[19] Particularly infections complicate the peri- and post-procedural period and amputation rates in CLI patients with diabetes are as high as 48% (compared to 37% in non-diabetics at Rutherford grade 6). Overall, the risk of amputation is increased 1.5-fold by diabetes during hospitalization for CLI (RF 6), and further 1.3-fold in the 4 years thereafter.[19]

Chronic kidney disease (CKD) is another common risk factor for the pathogenesis of BTK-PAD and its clinical progress to CLI. German data estimate CKD to be co-prevalent in 22-33% of CLI patients, compared to a prevalence of 14% in claudicants.[15] Concomitant CKD independently increases the risk of fatal long-term outcome in terms of death (HR 1.47), amputation (HR 1.12), and myocardial infarction (HR 1.3).

All these cardiovascular risk factors, further interacting with lifestyle factors such as unhealthy diet or physical inactivity have extensively been shown to predict polyvascular atherosclerotic manifestation. In fact, 60% of patients with PAD suffer of at least one other arterial territory undergoing arteriosclerotic pathological changes. Thereof manifestation of coronary artery disease is most common with a co-prevalence in almost every second PAD patient.[6] The history of other cardiovascular disease is highly predictive for the prevalence of PAD particularly in industrialized nations (LMIC OR 1.7; HIC OR 2.6; global 2.3.[6] Conversely, (detected) PAD is present in at least 10% of patients with coronary artery disease or cerebrovascular disease. Polyvascular disease affects approximately 1.6% of cardiovascular patients, corresponding to 13% of patients with PAD. The co-prevalence of arteriosclerosis in other than the peripheral arteries significantly worsens the prognostic outcome in PAD patients, since 40-60% of deaths in PAD are attributed to coronary events, and another 10-20% of deaths to cerebrovascular disease.[5] The disability-adjusted life years (DALYs) in PAD on a global perspective are highest in western and central Europe, Australasia, and North America (DALY >40), indicating high years of life lost due to death or disability in patients of these regions. DALY rates are further increased in the Caribbean, eastern Europe and Latin America (DALY 11-29), whereas Asia (5-13), Oceania (8), and east/west Sub-Saharan Africa (4-5) have lowest DALY burden against the background of comparably low general life expectancy.[20] In the big picture, however, the contribution of PAD to the global burden of disease is minor (around 1 million DALYs) as compared to *e.g.* ischemic heart disease (>100 million DALY).[21] In European countries, the direct health care costs for cardiovascular diseases sum up to 195,554,113,000 Euro. Thereof, alone 14% result of productivity loss of the chronically ill patients, further complemented by 10% for morbidity and mortality, and 54% of direct healthcare costs.[5] In Germany, costs for PAD and its sequelae amount to approximately 2.56 billion Euro, respective 7% of the annual 37 billion Euro health expenditures.

Prognosis of PAD

The prognosis of patients with PAD is strongly dependent on the stage of disease.[15] While in-hospital mortality in claudicants (Rutherford grades 1-3) is below 1%, it increases to 3.5% in patients with ischemic rest pain (RF 4) to further 8.3% in patients with ischemic tissue loss and gangrene (RF 6). Likewise, risk of in-hospital amputation increases dramatically from 0.5% in claudicants and 1.6% in pain at rest to 42% in CLI patients with gangrene at RF 6. However, the fate of claudicants already points out the malign nature of PAD and its common risk constellations: within 5 years, 20% of patients experience a deterioration towards higher stages, thereof one-third to CLI (5). Other studies show 4-year prognosis on unselected in-hospital treated claudicants to involve cumulative amputation rates of approximately 5% and cumulative mortality risk of approximately 20%.[15]

Finally, CLI is associated with fatally impaired prognosis: 1-year mortality ranges between 20-35%, amputation risk reaches 30-60% and only 30-45% of CLI patients are alive with both legs intact after 1 year.[5, 15] After 10 years, almost 90% of PAD patients at the stage of CLI (Rutherford 4-6) are deceased (Norgren, TASCII 2007).

These data highlight the importance of effective and consistent treatment in order to improve patient's prognosis. Current guideline recommendations argue for an interdisciplinary approach of a comprehensive therapy, including pharmacotherapy, preventive measures and life-style modification, and in particular urgent revascularization in critically ischemic states.

Analyses of data analyses of German health claims on German cohorts however indicate a presently existing huge shortage in supply with revascularization procedures in PAD patients at critical perfusion states. Against the background of almost 50% of patients being threatened of limb loss, application of overall revascularization in only 65% of patients appear clearly too reserved. Notably patients with concomitant diabetes were affected by this undersupply.[19] Whereas 75% of hospitalized claudicants received (any sort of) revascularization procedure, the

percentage decreased with increasing PAD stages to 70% in RF 4, 51% in RF 5 and only 49% in RF 6.[15] Major deficits concern amputated PAD patients: in a large-scaled analysis on unselected patients, only 45% received at least (any) attempt of revascularization prior to the amputation. Thus, over 37% of amputations were conducted without any angiography or revascularization attempt - neither during the respective hospitalization nor within the 2 years before.[15]

Facing the challenges that arise from these highly demanding patients, particularly those with BTK-PAD and critical limb ischemia, state-of-the-art invasive treatment is urgently needed to be provided area-wide at high quality levels.

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