

## **Gender Difference in Presentation and Outcome of PAD & CLI**

---

Historically, vascular disease in women has been both underdiagnosed and undertreated. Hence the majority of treatment outcome studies have been conducted in predominantly male cohorts with small subgroups of females. (Cheanvechai et al, 2004), (Gallagher et al, 2011)

While gender-related differences in coronary artery disease and stroke have been studied extensively, gender differences in PAD and CLI remain understudied. (McCoach et al, 2013)

Women with PAD represent a growing population of patients. It has been well documented in both the carotid and aortic literature that vascular disease in women differs significantly from men in the natural history, clinical characteristics, and physiologic patterns. (Gallagher et al, 2011), (McCoach et al, 2013)

Compared to men, women with PAD may present at an older age with atypical symptoms and more advanced atherosclerotic disease and have lower rates of bypass graft patency. Preliminary research has also suggested that women with PAD and CLI have worse long-term outcomes. (McCoach et al, 2013)

Contrary to common wisdom, elderly women do develop peripheral arterial disease (PAD), presumably because they are deprived from the

## Gender Differences in presentation and outcome of PAD & CLI

atheroprotective effect of female hormones in the postmenopausal years. This misperception has, in part, led to under-diagnoses and presentation with more advanced disease in women. According to older reports, women are also more likely to undergo amputation and are less likely to have an arterial reconstruction as a first-line procedure. (Egorova et al,2009), (Vouyouka et al, 2010)

### Prevalence and mean age:

Women present later in the disease process than men and thus have more advanced disease. (McCoach et al, 2013)

The mean age of women presenting with PAD is higher than that of men. (Kumakura et al, 2011)

Asymptomatic cases of PAD are more frequent among women than men. In contrast, the prevalence of IC tends to be higher in men, particularly for subjects aged 75–79 years old. (Kumakura et al, 2011), (Sigvant et al, 2007)

The lower prevalence of IC in women may be a consequence of slower progression of disease and less development of claudication due to lower levels of physical activity. (Collins et al, 2006)

Despite the observed differences in intervention indication, the determination of patient TASC classification showed no differences between males and females with respect to lesion characteristics. Reasons for this are unclear, as the presence of more CLI in the female group would be expected to correlate with more advanced TASC classifications. This finding may be a result of the subjective nature of CLI classification (which relies partially

## Gender Differences in presentation and outcome of PAD & CLI

on patient history of rest pain) and the more objective nature TASC classifications. It is conceivable that women report the presence of rest pain earlier in the progression of PAD when compared to men. This rationale is supported by the fact that when CLI-indication patients were broken down into rest pain and tissue loss subgroups, only rest-pain was significantly more prevalent in women. (Gallagher et al, 2011)

Research has suggested that there are basic gender differences in cardiovascular disease, some of which are attributable to the variable levels of estrogen in men and women. Estrogen appears to have a cardioprotective effect on vessel walls and lipid profiles. However, these effects abate after menopause, and it is unlikely that estrogen plays a significant role in improving the outcome of primarily postmenopausal cohort. (Gallagher et al, 2011)

When studying the influence of gender difference on the outcomes of infrainguinal bypass for critical limb ischaemia in Chinese patients, AhChong and colleagues also reported that women were older than men (median age 75 vs 70 years,  $p=0.001$ ) (AhChong et al, 2002)

When studying gender differences in patients treated for critical limb ischemia, Hultgren and colleagues reported that women had a higher mean age at time of intervention than men (74 vs 70 years). A later onset of disease might be a reason for the age difference between women and men, as has been shown for coronary heart disease. Protection by endogenous oestrogen could hypothetically explain the higher mean age in women treated for CLI. (Hultgren et al, 2005)

Natalia Egorova and colleagues identified 2.4 million LE inpatient PAD-related hospitalizations from 1998 through 2007 in Florida, New Jersey, and

## Gender Differences in presentation and outcome of PAD & CLI

New York; in 0.5 million of those hospitalizations, PAD was the primary diagnosis. The ratio of women to men was 46% vs 54% ( $P < 0.0001$ ). The rate of intervention was 56% for men vs 44% for women based on all PAD-related inpatient hospitalizations ( $P < 0.0001$ ) and 56% for men vs 53% for women based on hospitalizations with PAD as the primary diagnosis ( $P < 0.0001$ ). On average, women were older: mean age for all PAD-related hospitalizations was 73 years for women and 70 years for men ( $P < 0.0001$ ). PAD is less frequent in premenopausal and perimenopausal women because hormonal and metabolic factors create an atheroprotective environment, although the mechanisms are not well understood. However, PAD in women increases significantly during the postmenopausal years. The incidence of the disease in septuagenarian women and men is equal. (Egorova et al, 2009)

Among population who underwent intervention for PAD, in the study of Vouyouka and colleagues, women on average were older; the mean age for women was 72 and for men, 69 years ( $P < 0.0001$ ). (Vouyouka et al, 2010)

### Risk factor profile:

Compared to men, women with CLI have a higher composite rate of major adverse cardiovascular events (MACE). At the time of angiography women have a lower prevalence of known CAD and a higher baseline HDL than men. There are several potential explanations for MACE in women. First, this could be due to the continued lack of recognition of CAD in women, whether due to bias in diagnosis or differences in presentation compared with men. Second, women with PAD and CLI may have more extensive

## Gender Differences in presentation and outcome of PAD & CLI

overall atherosclerotic burden, thereby raising their rates of subsequent stroke and mortality. (McCoach et al, 2013)

Symptomatic conditions were more severe in women, including more frequent diabetes mellitus and hyperlipidemia. (Kumakura et al, 2011)

Cigarette smoking was commoner in men (83% vs 37%,  $p < 0.001$ ). (AhChong et al, 2002)

Spiros G. Frangos and colleagues reported no statistically significant difference between men and women, undergoing vein bypass graft, in the preoperative prevalence of diabetes mellitus, cardiac disease, tobacco use, hypertension, CVA, hypercholesterolemia, cancer, or renal status. (Frangos et al, 2000)

In the study of R. Hultgren and colleagues, there were fewer female diabetic patients and smokers, but other risk factors were similar. An explanation for the low prevalence of diabetes among women could be negative selection of women with diabetes. Women often have smaller vessels than men, and patients with diabetes tend to have worse run-off. This combination may have caused 'rejection' for surgical intervention. (Hultgren et al, 2005)

Among population who underwent intervention for PAD, in the study of Vouyouka and colleagues, women were more likely to be black, have hypertension and cerebrovascular disease, and at least twice as likely to be obese than men. Men, on the other hand, were more likely to be white, smokers, and had a higher prevalence of chronic obstructive pulmonary disease (COPD), DM, CAD, and renal disease. (Vouyouka et al, 2010)

## Gender Differences in presentation and outcome of PAD & CLI

### **Mode of presentation:**

Men in the study of Spiros G. Frangos and colleagues were more likely to have tissue loss as a preoperative diagnosis, whereas women had rest pain more frequently. (Frangos et al, 2000)

In the study of R. Hultgren and colleagues, number of patients admitted for urgent intervention was similar for women and men. Similarly, an equal proportion of women and men had rest pain at the time of intervention. (Hultgren et al, 2005)

In the study of Birgitta Sigvant and colleagues, asymptomatic PAD was more frequent among women ( $P = 0.03$ ) than men. Severe ischemia (ankle pressure  $\leq 70$  mm Hg with or without pain in the leg at rest) was also more common among women. This pattern was consistent for all age groups. Constitutionally higher ABI in women, smoking habits, postmenopausal hormonal effects, lower prescription rates of drugs to reduce risk factors, and smaller vessels could be possible explanations for this difference between men and women. IC prevalence tended ( $P = 0.09$ ) to be more common among men overall. This may be a consequence of the difference in walking habits and a general higher morbidity in women. (Sigvant et al, 2007)

When Natalia Egorova and colleagues studied gender related differences in peripheral arterial disease, they found that although women were less likely to be admitted for LE PAD, they were persistently more likely to be hospitalized emergently. In fact, 56% of women vs 51% of men with primary PAD diagnoses were hospitalized emergently in 1998 and 57% vs 53% in 2007. The difference between these trends was constant throughout

## Gender Differences in presentation and outcome of PAD & CLI

the decade ( $P = 0.0001$ ). Also, women had a higher frequency of CLI per PAD-related hospitalization (Egorova et al, 2009)

Among population who underwent intervention for PAD, in the study of Vouyouka and colleagues, women were more likely to be treated for advanced PAD associated with CLI. The reasons for this are not well understood, but certain speculations could be made. The early symptoms and signs of PAD in women may go unnoticed, because there is an established bias in society and among physicians that women do not get atherosclerotic disease. This is in part true for young women during the reproductive years when hormonal and metabolic factors are causing an atheroprotective physiologic environment. However, elderly women are deprived from this beneficial effect of reproductive hormones and are at least as likely as men to develop atherosclerotic disease. There are also other possible factors that do not allow prompt medical treatment of vascular disease in women. Elderly women with PAD are more likely than men to live alone, be isolated or live in extended care facilities or care for an even older and more disabled spouse and, therefore, often neglect their own symptoms. (Vouyouka et al, 2010)

Lower income and higher poverty rates among elderly women are associated with more advanced PAD and 1.4-fold increase in amputation rates compared with higher-income patients. (Vouyouka et al, 2010)

Symptoms related to arterial disease in elderly women are often masked by those related to osteoporosis or degenerative joint disease, which are also prevalent in this particular group of patients. (Vouyouka et al, 2010)

## Gender Differences in presentation and outcome of PAD & CLI

Compared with men, women are hospitalized for treatment at more advanced stages of their disease and require emergency and not elective medical attention, or they have a more complicated course during the management of their disease that causes clinical situations that cannot be treated electively. (Egorova et al, 2009)

PAD in women may go unrecognized until it reaches a critical stage. There are several reasons why PAD might be unrecognized in women compared with men:

- women with PAD are usually older and may be socially isolated;
- they may be taking care of a sicker, older husband and thus neglect their own medical needs;
- they tend to have lower income, which hinders them from seeking specialized medical care; and
- their symptoms of early arterial insufficiency might be mistaken for other conditions such as osteoporosis or arthritis, which are also frequent in older women. (Egorova et al, 2009)

### Regional lesion characteristics:

Women are more likely to have femoropopliteal disease as well as multi-level infrainguinal disease, while men with CLI are more likely to have iliac lesions. (McCoach et al, 2013) (Kumakura et al, 2011)

When focusing on femoropopliteal lesions and their characteristics, it was found that though there were no differences in the TASC II classification,



## Gender Differences in presentation and outcome of PAD & CLI

women demonstrated less severe lesion calcification. For infrapopliteal disease there is no gender-based differences in baseline lesion characteristics. (McCoach et al, 2013)

When studying the influence of gender difference on the outcomes of infrainguinal bypass for critical limb ischaemia in Chinese patients, A. K. AhChong and colleagues found that the caliber of arteries at the distal anastomosis site was smaller in females than males (median 2.45mm vs 2.01mm,  $p=0.03$ ) (AhChong et al, 2002)

In the study of R. Hultgren and colleagues, the localisation of the treated lesions differed between women and men, more suprainguinal lesions were treated in women (44% in women vs 19% in men). (Hultgren et al, 2005)

When Natalia Egorova and colleagues studied gender related differences in peripheral arterial disease, they found that women were more likely to have a more advanced disease: they were persistently less likely than men to have claudication ( $P= .0002$ ). (Egorova et al, 2009)

### **Treatment modality:**

Natalia Egorova and colleagues noticed a remarkable and continuous growth of endovascular procedures in the last 10 years distributed equally in both genders. Endovascular procedures were the most frequently performed vascular interventions in both genders, with comparable rates. The equal utilization of endovascular procedures in both sexes might have contributed to the diminished sex-related disparity in amputation rates that was observed in their study. (Egorova et al, 2009)

## Gender Differences in presentation and outcome of PAD & CLI

Amaranto et al determined that gender was not a determinant of intervention for both PAD and carotid artery disease. (Amaranto et al, 2009)

Vouyouka and colleagues stated that among 372,692 hospitalizations in which at least one procedure for PAD was performed, procedures were performed more often on men (56%) than women (44%). (Vouyouka et al, 2010)

### **Outcome:**

Women are more likely to undergo multi-level infrainguinal interventions and develop infrapopliteal restenosis after endovascular intervention, yet major amputation rates are similar between women and men, and this supports the hypothesis that restenosis is not directly linked to an increased risk of amputation. (McCoach, C. E. et al, 2013), (Romiti et al, 2008)

The prevalence of treatment with medication is higher in women than men. (Kumakura et al, 2011)

When the indication for endovascular treatment is CLI, females do significantly better in both the SFA and tibial vessels following both primary angioplasty and angioplasty with stenting compared with males. The reasons for this trend are unknown; however, it is possible that there is a biologic explanation for these findings. (Gallagher et al, 2011)

The median period of hospital stay was longer in females compared to males (median 32 vs 25 days,  $p=0.02$ ) following infrainguinal bypass surgery in Chinese patients. (AhChong et al, 2002)

When analysed according to gender, Chinese female patients had significantly inferior primary graft patency following infrainguinal bypass

## Gender Differences in presentation and outcome of PAD & CLI

surgery in comparison to that of men. Also, secondary patency rates were 64% and 35% at 3 years for men and women respectively. However, the lower secondary graft patency in women did not lead to inferior limb salvage rate. (AhChong et al, 2002)

Following infrainguinal bypass surgery, Spiros G. Frangos and colleagues reported that women were more likely to develop incisional complications that included wound infection, wound dehiscence, or ischemia/necrosis at the incision site. There was no significant difference between men and women for primary patency ( $P = 0.573$ ), secondary patency ( $P = 0.787$ ), limb salvage ( $P = 0.402$ ), or survival rates ( $P = 0.445$ ). (Frangos et al, 2000)

In the study of R. Hultgren and colleagues, mortality and amputation rates, were similar in women and men over time. Minor secondary procedures (defined as a minor surgical procedure, such as toe exarticulation or ligation of AV fistulas from a vascular graft) were performed in a similar proportion of women and men. Postoperative bleeding was similar, but infection tended to be more common in men (7% vs 12%,  $p=0.08$ ). Length of hospital stay was 11 days for women (0–37) and 9 days for men (0–59),  $p=0.19$ . The frequency of postoperative graft occlusion (19% vs 16%,  $p=0.35$ ) and anastomotic or graft stenosis (5% vs 8%,  $p=0.27$ ) were also similar. (Hultgren et al, 2005)

Among population who underwent intervention for PAD, in the study of Vouyouka and colleagues, women had notably higher rates of bleeding (10.6% vs 8.2%;  $P < 0.0001$ ) and postoperative mortality (5.26% vs 4.21%;  $P < 0.0001$ ) and were more likely to undergo a major leg amputation during a lower extremity revascularization hospitalization (24.9% vs 23.4%;  $P < 0.0001$ ) than men. (Vouyouka et al, 2010)

## Gender Differences in presentation and outcome of PAD & CLI

Overall, women had a higher risk of perioperative infection (3.23% vs 2.88%;  $P = 0.0001$ ). (Vouyouka et al, 2010)

Bleeding is more common in women than men for all of the procedures performed for PAD. The difference was greatest for hospitalizations in which both open and endovascular procedures were performed (15.74% vs 10.92%;  $P < 0.0001$ ). (Vouyouka et al, 2010)

Natalia Egorova and colleagues reported in their study that it is unclear why women have higher procedurally related mortality rates than men. One explanation may be more advanced age. In multivariable analysis, female gender did not increase the risk of death after open and endovascular reconstructions of octogenarians and had a protective effect for those undergoing amputations. Female gender increased the risk of periprocedural mortality of younger patients. Given that risk factors for this latter group are not well understood, it is possible that failure to manage these risk factors contributed to this observation. The gender effect on mortality is not seen in octogenarians because these patients are more homogeneous in terms of comorbidities and risk factors due to a natural selection that occurs in such advanced age. (Egorova et al, 2009)

Overall mortality for all PAD procedures was 1.1% higher for women than men. Interestingly, advanced age alone dissipates the negative effect of female gender on periprocedural mortality, gender has no negative effect on mortality in octogenarians. (Vouyouka et al, 2010)