Disproportionate Gender and Racial Representation in Clinical Studies Involving Drug-Coated Balloon Devices in PAD/CLTI

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Abstract

Objectives: Despite a recent increase in research efforts regarding disparities in peripheral arterial disease/critical limb-threatening ischemia (PAD/CLTI), few studies have focused on minority and women participation in late-breaking clinical investigations exploring various treatments for PAD/CLTI. We seek to explore the representation of minority groups and women in clinical studies evaluating the usage of drug-coated balloons (DCBs) for treatment in PAD/CLTI. **Methods:** A review of all US-based studies investigating DCBs in PAD/CLTI registered on ClinicalTrials.gov with results was recorded. Several combinations of DCB and PAD were used as identifying key terms. Demographic and gender characteristics were analyzed and compared with the 2020 US Census as well as the estimated prevalence of PAD/CLTI in the US population for the year 2000. **Results:** Of the many studies, 4 clinical trials investigating the efficacy of DCBs in PAD/CLTI were identified based on the inclusion criteria; however, only 3 reported race and/or ethnicity information. Of 1816 total participants, 34% were women and 66% were men. All minorities were underrepresented, while the population of White patients was comparable to the 2020 US Census data. Additionally, when correlated with the prevalence rates of PAD/CLTI in the year 2000, nearly all populations recorded in this study reported disproportionate findings, with the exception of the White patient population being analogous. **Conclusions:** Women and all racial minority groups in US-based studies evaluating the usage of DCBs for PAD/CLTI were grossly underrepresented. These findings bring to question the real-world validity of such studies and suggest diverse enrollment strategies be a required focus during recruitment.

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Peripheral arterial disease/critical limb-threatening ischemia (PAD/CLTI) is a disorder in which arteries in the lower extremities become occluded. The prevalence of PAD/CLTI has increased year after year, and as of 2015, it is estimated that well over 236 million people worldwide have PAD/CLTI.[1] Many individuals with PAD/CLTI go undiagnosed for years until the condition becomes severe.[2] Initial treatments for PAD/CLTI include exercise therapy and risk modification by managing a patient's comorbidities, including diabetes, dyslipidemia, and hypertension. However, patients who present with severe claudication or PAD/CLTI that is refractory to conservative management will have to undergo revascularization procedures. Interventional treatments for severe and refractory PAD/CLTI have made leaps and bounds in recent years with major innovation in creating new endovascular technology in drug-coated balloons (DCBs) containing the antiproliferative agent paclitaxel. The latest DCBs are capable of opening up stenotic arteries and restoring blood flow while preventing restenosis in previously difficult-to-reach arteries.

Despite the promising evidence, however, a meta-analysis by Katsanos et al.[3] in 2018 rattled the endovascular field with alarming claims of paclitaxel-coated devices being associated with higher mortality rates at years 2 through 5 compared with non-paclitaxel-coated devices. The study also reported a positive dose-response relationship between increasing paclitaxel doses

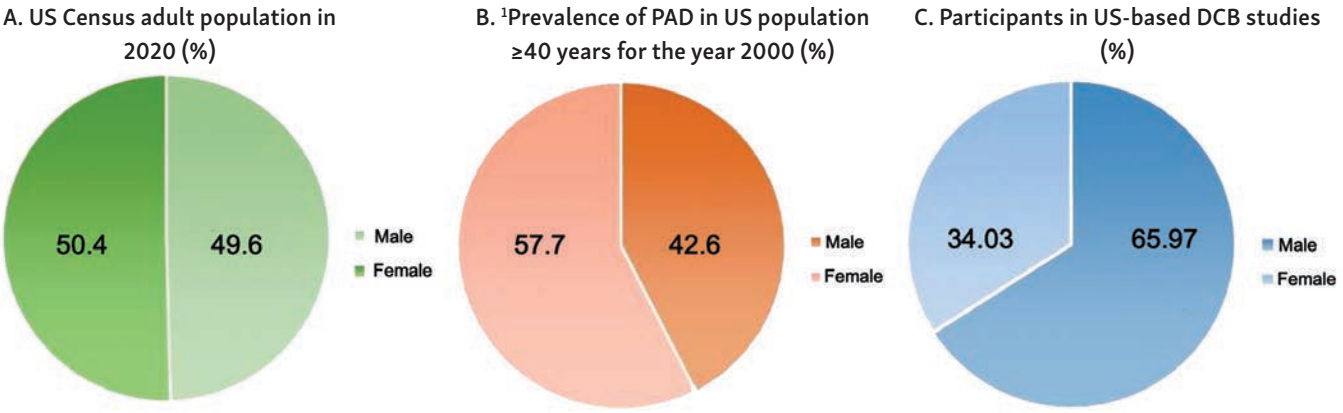

FIGURE 1. A comparison of US gender demographics: A) The general US adult population is essentially evenly split between men and women. B) Peripheral arterial disease (PAD) affects significantly more women than men in the US population. C) Despite females accounting for the majority of PAD cases in the US, they are disproportionately underrepresented in US-based drug-coated balloon studies.

Data derived from Allison MZ, HoE, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Med. *2007;32:328-333.*

and absolute risk of mortality. This contentious report was followed by an investigation by the Food and Drug Administration (FDA) advisory panel concluding similar findings and issuing warnings on paclitaxel-coated devices having possible increased mortality.[4] Subsequently, important lessons in the study designs of vascular device trials emerged from this controversy, including improved long-term follow-up strategies and data collection. However, it appears that a vital topic regarding diversity among trial participants in such studies was masked by how prominent the paclitaxel dispute existed in literature for the past 5 years.

Conversely, when evaluating the field of PAD/CLTI research, much attention has been focused on racial and gender disparities in the prevalence and management of PAD/CLTI. Accordingly, studies have concluded pre-existing challenges for minorities and women that affect their access to adequate PAD/CLTI care, especially from factors involving language and transportation.[5] Given this prior knowledge and recent controversy, it brings to question whether disparity may be present in the randomized clinical trials (RCTs) performed to study new, innovative treatment devices for PAD/CLTI. Our study aims to assess a number of recent clinical trials for DCBs in the treatment of PAD/CLTI and explore the representation of minority groups and women in such studies. Recognizing and addressing disparities is critical to ensuring that PAD/CLTI patients of all genders and races are screened, treated, and properly managed with long-term follow-up in an equitable manner.

Methods

A query on ClinicalTrials.gov was conducted to obtain all US-based studies involving DCB utilization in PAD/CLTI therapy. Several word combinations of DCB and PAD/CLTI were used as identifying key terms by 2 independent teams to attain a thorough inquiry of clinical studies. Data on participants was obtained from information published in the results section of individual trials. Demographic and gender characteristics were collected. Inclusion criteria included initial studies comparing the use of DCBs against standard balloon angiography.

Demographics from the 2020 US Census population and the estimated prevalence of PAD/CLTI by ethnicity in the US population age 40 years or older for the year 2000 were obtained and extrapolated. Demographics and gender were reported as frequencies for categorical variables. Data was analyzed descriptively, comparing mean percentage to the US Census and extrapolated data from Allison et al.[6] A two-sample Z test of proportion comparing the population results from each demographic was used to investigate statistical differences. A multidisciplinary committee of statisticians, vascular surgeons, interventional cardiologists, and interventional radiologists was selected to independently review, calculate, analyze, and recheck all study-related analyses to confirm the findings. The visual table was designed using Excel software version 365 ProPlus (Microsoft). $P<.05$ was considered statistically significant.

Results

A total of 4 clinical trials (Stellarex DCB by Philips,[7] Lutonix DCB by Bard,[8] In.Pact Admiral DCB by Medtronic,[9] and Ranger DCB by Boston Scientific[10]) investigating the safety and effectiveness of DCB utilization in PAD/CLTI therapy were identified based on the inclusion criteria. Of the 4 studies, only 3 reported race and/or ethnicity information. From the total study population of 1816 participants, 34.03% were women and 65.97% were men. Distribution by gender was compared to 2 separate groups in **Figure 1**. Despite the higher prevalence of PAD in women, with 57.7% affected compared with 42.6% of men, US DCB studies exhibited

TABLE 1. RACE DISTRIBUTION OF US DRUG-COATED BALLOON STUDIES VS GENERAL POPULATION

Race and gender distribution	Participants in US-based DCB studies (%)	US Census adult population in 2020 (%)	*P* value
Black	3.30	13.60	<.001
White	77.64	75.50	.134
Hispanic	3.74	19.10	<.001
Asian	11.29	6.30	<.001
Native Hawaiian or other Pacific Islander	0.21	0.30	.352
American Indian or Alaska Native	0.11	1.30	<.001
Other	3.19%		

Black and Hispanic populations are heavily underrepresented in drug-coated balloon (DCB) studies. Combined, they make up only 7% of DCB-study participants despite accounting for one-third of the total US adult population.

TABLE 2. RACE DISTRIBUTION OF US DRUG-COATED BALLOON STUDIES VS RACE DISTRIBUTION OF US PERIPHERAL ARTERIAL DISEASE PREVALENCE

Race and gender distribution	Participants in US-based DCB studies (%)	[1]Prevalence of PAD in US Population ≥40yrs for the year 2020 (%)	*P* value
Black	3.30	15.90	<.001
White	77.64	78.3	.363
Hispanic	3.74	38.0	<.001
Asian	11.29	15.3	<.005
Native Hawaiian or other Pacific Islander	0.21		
American Indian or Alaska Native	0.11	0.73	.021
Other	3.19		

Similarly to how US drug-coated balloon (DCB) studies underrepresented Black and Hispanic populations compared with the general US population, these studies also demonstrate similar disparities when compared with the general peripheral arterial disease population in the US.

Data derived from Allison MZ, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Med. *2007;32:328-333.*

a notable gender discrepancy. Specifically, a larger proportion of men, comprising 65.97% of participants, were involved in these studies compared with women, who represented only 34.04% of the participants. Among the trial participants, approximately 77.64% were White, 3.30% were Black, 3.74% were Hispanic, 11.29% were Asian, 0.21% were Native Hawaiian or other Pacific Islander, 0.11% were American Indian or Alaska Native, and 3.19% were classified as "other". **Table 1** and **Table 2** describe a side-by-side comparison of trial participants to the 2020 US Census and the 2000 study of PAD/CLTI prevalence in the US age 40 and over by distribution of race, respectively. In comparison with the broader US adult population, which comprises 13.6% Black individuals and 19.1% Hispanic individuals, US DCB studies reflect significantly lower representation of these groups, accounting for only 3.30% and 3.74% ($P<.001$, $P<.001$), respectively. This discrepancy becomes even more pronounced when considering the demographics of individuals affected by PAD, where Black patients constitute 15.9% and Hispanic patients account for 38.0% of the affected population. Interestingly, while the general population includes 6.3% Asian individuals, US DCB studies feature a higher proportion, with 11.29% of participants being Asian. However, this trend reverses when compared with the PAD-affected population, where Asian patients represent 15.3%, indicating a disparity in the representation of Asian individuals in US DCB studies compared with the actual demographic distribution among PAD patients.

Discussion

Since the passing of the National Institutes of Health Revitalization Act in 1993,[11] multiple efforts from federal agencies, including the Centers for Disease Control and Prevention, FDA, and the Agency for Health Research and Quality have followed suit in creating initiatives to improve participation and recruitment of minorities and women in clinical trials.[12,13]

Despite these efforts, several studies have consistently noted a lack of race and/or ethnicity reported in RCTs, as well as repeated underrepresentation of women and minorities in these populations.[11,12,14] Our study aligns with previous and current literature, which consistently highlights the underrepresentation of marginalized groups in clinical studies.

In this study, the participants of randomized DCB trials from minority groups, including Black, Hispanic, Native Hawaiian/Pacific Islander, and American Indian/Alaska Native patients, were all below the 2020 US Census demographic population levels, respectively. Similarly, women participants in the study were lower than the gender breakdown reported in the US Census. These findings persisted with data correlation to Allison et al's[6] prevalence of PAD/CLTI in the US population. In this parallel, all minorities and women participants in the study recorded lower numbers, further suggesting possible ineffectiveness in the recruitment and enrollment strategies for RCTs. Interestingly, despite a higher prevalence of PAD/CLTI recorded by Allison et al[6] in the Hispanic population, the percentage of study participants represented for this group remained similar to that of Black individuals. White participants in the randomized DCB

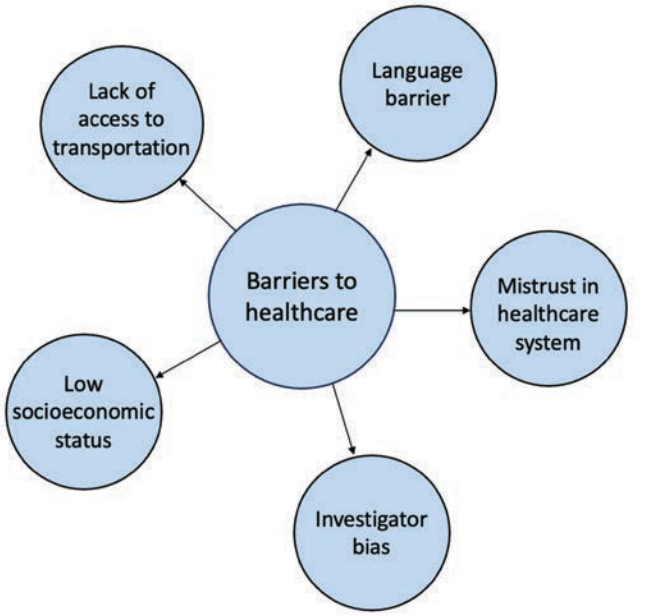

FIGURE 2. Social determinants of health care access. Interconnected barriers affecting health care accessibility include low socioeconomic status, transportation constraints, mistrust in the health care system, limited medical and research literacy due to language barriers, and investigator bias.

trials were consistently well-represented and comparable in both datasets.

Various barriers to healthcare displayed in **Figure 2** have been highlighted as possible challenges and reasons for reduced participation in clinical trials. Low socioeconomic status, lack of access to transportation, mistrust in the health care system, limited medical and research literacy due to language barriers, and investigator bias are major social determinants of health contributors.[13] Importantly, mistrust in clinical research and medical science has historically remained a notable difficulty in the recruitment of minorities and women. Stemming from centuries of mistreatment in clinical research and the amount of implicit bias deeply rooted in medical practices, several minorities and women firmly believe in the possibilities of exploitation and harm that may exist toward them in the health care system.[15] As a consequence, communities affected by years of mistreatment are deterred from participating in trials and research studies.

Additionally, studies have highlighted linguistic barriers and lack of transportation to be considerable obstacles to health care access, especially in Hispanic populations diagnosed with PAD/CLTI.[5] This, along with many other health determinants, hinders proper contact with quality health care in many underserved and minority communities. At its core, office-based labs (OBLs) carry promising potential to mediate the many barriers associated with social determinants of health by providing safe, efficient, cost-effective, and affordable care compared with big hospital systems, which are often limited to major urban areas. However, increased criticism in recent news has possibly diverted attention from the potential solutions OBLs address with decreased accessibility to care as well as challenges in diverse participation in clinical research. Because there are substantial hurdles for minorities and women, possibly stemming from strict requirements such as multiple follow-up appointments and consistent clinical visits, leveraging the convenient locations of OBLs may be vital in driving increased diversity in RCT participation.

Health disparities in PAD/CLTI are not new or unknown. Collectively, minorities and women experience a larger degree of social obstacles compared with their counterparts, leaving these groups at an increased disadvantage in receiving access to health care. Black individuals are disproportionately affected by PAD/CLTI, with nearly 1 in 3 Black adults at risk for developing this debilitating leg disease.[16] For those where amputation is absolutely necessary for treatment, Black, Hispanic, and American Indian adults report decreased survival rates and experience worse quality of life compared with White adults post amputation.[18] Additionally, sex differences in PAD/CLTI are apparent yet underrecognized in clinical practices and research. Women have reported worse outcomes and equal if not greater prevalence of PAD/CLTI in recent data, contrary to previous findings and/or beliefs.[17]

Along with these existing disparities in PAD/CLTI, our study indicates the continued lack of minority and women representation in clinical research trials geared toward treatment modalities in PAD, particularly with the utility of DCBs. To date, only 1 global, prospective, multicenter registry, the ELEGANCE trial, is dedicated to collecting real-world data from diverse groups, particularly focusing on women and underrepresented minorities in the PAD/CLTI population.[18] This trend, aligned with background knowledge of PAD prevalence rates by gender, race, and ethnicity, should be a required focus to improve the development of appropriate treatment devices and increase generalizability for the populations served.

Conclusion

In this new era of PAD/CLTI endovascular care driven by data, evidence-based practices, and collaboration, it is difficult to improve and innovate what we do not measure. Women and all racial minority groups in US-based studies evaluating the usage of DCBs for PAD/CLTI were grossly underrepresented in comparison to the US Census and the predicted prevalence rate of PAD. These findings bring to question the real-world validity of such studies and suggest diverse enrollment strategies be a required focus during recruitment. Conscious efforts from investigators must be made to increase the representation of minorities and women to progress the cutting-edge PAD/CLTI research for all real-world populations.

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