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Peripheral Artery Disease as a Prognostic Factor for Amputation in Type 2 Diabetes Mellitus: An Evidence-Based Case Report

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Abstract

Myocarditis defined as inflammation of myocardium in response to acute injury. It can cause general and unclear symptoms. On ECG, it may show ST-segment elevation, which often mimicking ACS. Meanwhile, Wolff Parkinson White syndrome is a pre-excitation cardiac condition that is characterized by an accessory conduction pathway that predisposes individuals to tachyarrhythmias, including supraventricular tachycardia. When both conditions co-exist, diagnosis and management become particularly challenging. A 20-year-old male was admitted to our hospital with palpitations and diaphoresis 8 hours prior to admission, after playing soccer a night before, accompanied with shortness of breath and crushing chest pain. History of recent viral infections were denied. His initial BP was 100/70 mmHg and HR was 200 beats per minute, with normal physical examination. Admission ECG showed AVRT orthodromic. After vagal maneuver, ECG converted to sinus rhythm with ST elevation on inferior leads and suggesting WPW syndrome, troponin level was elevated. Coronary angiography revealed normal coronary arteries except for myocardial bridging in LAD. CRP and ASTO titers were elevated. Cardiac MR and endomyocardial biopsy were not done yet. This patient then diagnosed with WPW syndrome and suspected myocarditis. In WPW patients, the conduction of electrical pulses is no longer limited to the AV pathway due to the presence of accessory pathway, Bundle of Kent, that has considerable potential to cause supraventricular arrhythmias, which the important route is the AVRT route. In this case, myocarditis is thought to be the cause. Myocarditis can trigger arrhythmias due to various factors, including alteration of cardiac structural, vascular involvement, and changes in membrane potential triggered by inflammation. This case report highlights that myocarditis can act both as a substrate and a trigger for SVT in patients with WPW syndrome. When SVT occurs in WPW patients, we should consider myocarditis as the underlying cause. Early recognition could guide to appropriate management and prevent potential complications associated with both arrhythmia and myocardial inflammation.

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Keywords: myocarditis, Wolff-Parkinson-White syndrome, supraventricular tachycardia, ST-elevation

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Introduction

Diabetes mellitus (DM) is a lifelong chronic disease caused by metabolic disturbances in the pancreas, characterized by hyperglycaemia resulting from reduced insulin production (WHO, 2024). Type 2 diabetes mellitus (T2TM) develops through a combination of genetic and environmental factors (Antar et al., 2023; Kolb & Martin, 2017). Global prevalence of type 2 diabetes is projected to increase to 7079 individuals per 100,000 by 2030, reflecting a continued rise across all regions of the world. In 2022, 14% of adults aged 18 years and older were living with diabetes, an increase from 7% in 1990. Diabetes was the direct cause of 1.6 million deaths and 47% of all deaths due to diabetes occurred before the age of 70 years in 2021. There are concerning trends of rising prevalence in lower-income countries (Khan et al., 2020; WHO, 2026). The prevalence of diabetes in Indonesia is among the highest in the world. Data from the International Diabetes Federation shows that the prevalence of diabetes in adults reaches 11.3%. Among these cases, Type 2 Diabetes Mellitus is the most prevalent, accounting for approximately 50.2% of the total number of sufferers, according to the Indonesian Health Survey (SKI) report (Kemenkes BKPK, 2023).

Chronic hyperglycaemia results in macrovascular and microvascular complications. Macrovascular complications include myocardial infarction, stroke, peripheral vascular disease and diabetic foot. There is an increase in five-year mortality in patients diagnosed with macrovascular complications (Aikaeli et al., 2022). One significant complication of diabetes is diabetic foot ulcer (DFU), which increases morbidity and reduces quality of life. Diabetic foot ulcers are classified into three types: neuropathic, neuroischemic, and ischemic (Packer et al., 2023). In Indonesia, approximately 15% of individuals with diabetes develop DFU, and 30% of these cases progress to amputation (Azizah et al., 2019). Amputation is generally indicated when the ulcer fails to heal or when gangrene and infection occur simultaneously (Liao et al., 2022).

A study at Dr. Kariadi Hospital in Semarang identified independent risk factors for lower-extremity amputation among diabetic foot ulcer patients, including HbA1c ≥ 8%, the presence of peripheral artery disease (PAD), hypertriglyceridemia, and hypertension (Pemayun et al., 2015). PAD is an atherosclerotic condition affecting non-coronary arteries, where narrowing or occlusion reduces blood flow to the limbs (Criqui et al., 2021). Individuals with diabetes experience more severe PAD than those without diabetes. PAD is a major contributor to impaired wound healing, tissue necrosis, and gangrene (Nishio et al., 2021). Severe circulatory impairment can lead to tissue necrosis (gangrene), persistent infection, and inability of wounds to heal, all of which increase the risk of amputation (Akkus & Sert, 2022).

The development of diabetic foot ulcers typically occurs in three stages. The initial stage involves callus formation, often triggered by neuropathy. Motor neuropathy leads to foot deformities, while sensory neuropathy reduces protective sensation, resulting in repeated unnoticed trauma. Autonomic neuropathy also contributes by causing skin dryness. Recurrent trauma to callused areas can cause subcutaneous bleeding and eventually ulceration (Parveen et al., 2025; Strukel & Rai, 2025). Additionally, diabetes can cause significant atherosclerosis in small vessels of the lower limbs, impairing perfusion and delaying wound healing. This can eventually progress to necrosis and gangrene (Bhargava et al., 2023). Early detection and optimal treatment improve the prognosis, but delayed care may result in serious complications, including limb amputation (J. Kim et al., 2025). People with diabetes are at higher risk of developing atherosclerosis, the leading cause of PAD. Diabetes is responsible for most non-traumatic major and minor amputations globally (Schmitt et al., 2022).

The clinical relationship between DFU and lower-extremity amputation (LEA) is multifactorial and complex. LEA represents one of the most devastating and costly complications of type 2 diabetes mellitus and is widely regarded as a major adverse clinical outcome of diabetic foot disease. LEA is associated with permanent disability, impaired mobility, reduced quality of life, psychological distress, loss of independence, and a substantial socioeconomic burden for patients, families, and healthcare systems. Furthermore, patients who undergo major lower-extremity amputation experience high rates of postoperative morbidity and mortality, with five-year survival comparable to that of several common malignancies (Rusu et al., 2024). Importantly, most diabetes-related amputations are preceded by potentially preventable conditions, including foot ulceration, peripheral neuropathy, peripheral artery disease, infection, and delayed access to appropriate care. Evidence suggests that timely identification of high-risk patients, comprehensive foot assessment, optimization of glycaemic and cardiovascular risk factors, early vascular evaluation and revascularization when indicated, and multidisciplinary diabetic foot management can substantially reduce the incidence of avoidable amputations (Rathnayake et al., 2020).

Consequently, it remains challenging to determine the extent to which PAD independently predicts amputation after accounting for these coexisting risk factors. Therefore, a critical appraisal of the current evidence is needed to determine whether PAD independently predicts lower-extremity amputation in adults with T2DM and to assess the applicability of this evidence to clinical decision-making and limb-preservation strategies, particularly in resource-variable healthcare settings.

Clinical Scenario

A 45-year-old male with a seven-year history of type 2 diabetes mellitus presented to the clinic with a right foot ulcer. He also reported cramps and muscle pain in his legs that worsened with activity and improved with rest, along with a sensation of heat in the sole of his foot. He was subsequently diagnosed with peripheral artery disease. The patient expressed anxiety and concern about the possibility of amputation due to his diabetes and peripheral arterial condition.

Clinical Question

In adult individuals with type 2 diabetes mellitus, does prior peripheral artery disease serve as a predictor factor that elevates the risk of amputation? (based on PICO in table 1)

Methods

Article Search Methods and Strategy

A literature search was performed across three major databases: PubMed, ProQuest, and Cochrane on March 2025. The strategy search terms of each database showed in table 2. Initial article selection was based on the duplicate publications, that were identified by two reviewers using the Mendeley application. Only the latest version with the most comprehensive data retained. Then, articles were selected by relevance of titles and/or abstracts to these keywords. A manual search of the identified studies was then conducted to verify their suitability for inclusion in the critical appraisal. Articles were further screened for alignment with the research topic by reviewing their titles, abstracts, methodologies, and study designs. Only studies that met the inclusion criteria and addressed the clinical question structured using the PICO (Patient, Intervention, Comparison, Outcome) framework were included. PICO components were defined using core keywords, Medical Subject Headings (MeSH), and related synonyms for each element.

Eligibility Criteria

The inclusion criteria consisted of systematic reviews, meta-analyses of prognostic studies, and cohort or survival studies involving adult patients with diabetes and peripheral artery disease, as well as studies evaluating amputation risk among individuals with both conditions. Only articles published within the past 10 years were considered. Exclusion criteria encompassed studies without full-text availability, animal studies, papers lacking an abstract, and those employing study designs outside the specified criteria.

Critical Review Method

A critical assessment of the selected studies was performed using an Oxford prognostic evaluation worksheet (Oxford, 2011). Two reviewers conducted the initial evaluation, with a third reviewer acted as a mediator to resolve any discrepancies in assessments. An additional reviewer served as a proofreader to ensure clarity and accuracy in the final writing. Data extraction was performed by investigators using Microsoft Excel. Study results encompass the proportion, p-value (significant if <0.05), and the strength of association (odds ratio/OR or hazard ratio/HR) between factor and outcome.

The appraisal process consisted of three key components: validity, relevance of the findings, and applicability to clinical practice. The patient population in each study needed to be comparable and clinically meaningful. The results were evaluated based on their usefulness in real-world practice, with particular attention to whether the study population reflected the types of patients typically encountered in clinical settings. The level of evidence criteria used in this study refer to the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence guidelines (table 3)(Oxford, 2011).

Result

The literature search was conducted in three electronic databases: PubMed (n = 338), Cochrane Library (n = 2), and ProQuest (n = 65), yielding a total of 405 records (figure 1). These records were initially screened by title and abstract to determine their relevance to the clinical question regarding peripheral artery disease (PAD), type 2 diabetes mellitus (T2DM), and lower-extremity amputation (LEA). During the first screening stage, 372 articles were excluded because they did not investigate the target population, exposure, or outcome of interest. Consequently, 33 articles remained for further evaluation. The full texts of these 33 potentially eligible articles were then assessed against the predefined inclusion criteria. Following this assessment, 30 studies were excluded, primarily because they employed inappropriate study designs that did not address the prognostic question. As a result, 2 studies fulfilled all eligibility criteria. To ensure that no important evidence was missed, a manual search of the reference lists of the eligible studies was performed, identifying 2 additional articles. After evaluating these references, because it did not satisfy the eligibility criteria. Therefore, the final evidence synthesis consisted of 2 cohort studies. All two cohort studies demonstrated a moderate level of evidence (level of evidence 2).

Table 1. definition Term of

Problem	Intervention	Comparison	Outcome
• Adult • Diabetes Mellitus Type 2 • Type 2 Diabetes Mellitus • Diabetes Mellitus Type II • Type II Diabetes Mellitus	• Peripheral artery disease • Peripheral arterial disease	Without peripheral artery disease	• Amputation • Surgical Amputation

Table 2. Search Strategy of Each Database

Database	Search strategy	Hits	Selected articles
Pubmed	*(((((((((((((((((adult[MeSH Terms]) OR (adult[Title/Abstract])) OR (Diabetes Mellitus Type 2[MeSH Terms])) OR (Diabetes Mellitus Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[MeSH Terms])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Type II[MeSH Terms])) OR (Diabetes Mellitus Type II[Title/Abstract])) OR (Type II Diabetes Mellitus[MeSH Terms])) OR (Type II Diabetes Mellitus[Title/Abstract])) AND (Peripheral artery disease[MeSH Terms])) OR (Peripheral artery disease[Title/Abstract])) OR (Peripheral arterial disease[MeSH Terms])) OR (Peripheral arterial disease[Title/Abstract])) AND (Amputation[MeSH Terms])) OR (Amputation[Title/Abstract])) OR (Surgical Amputation[MeSH Terms])) OR (Surgical Amputation[Title/Abstract])*	338	1
Cochrane	#1 [Diabetes Mellitus, Type 2] #2 [Peripheral Arterial Disease] #3 [Amputation, Surgical] #4 [#1 and #2 and #3]	2	0
ProQuest	*(abstract(adult) OR abstract (Diabetes Mellitus Type 2) OR abstract (Type 2 Diabetes Mellitus) OR abstract (Diabetes Mellitus Type II) OR abstract (Type II Diabetes Mellitus)) AND (abstract (Peripheral artery disease) OR abstract (Peripheral arterial disease)) AND (abstract (Amputation) OR*	65	1

	abstract (Surgical Amputation))

Table 3. 2011 OCEBM Levels of Evidence for Prognostic Study

Level	**Type of evidence**
Level 1	Systematic review of inception cohort studies
Level 2	Inception cohort study
Level 3	Cohort study or control arm of randomized trial
Level 4	Case-series or case-control studies, or poor quality prognostic cohort study
Level 5	Not applicable

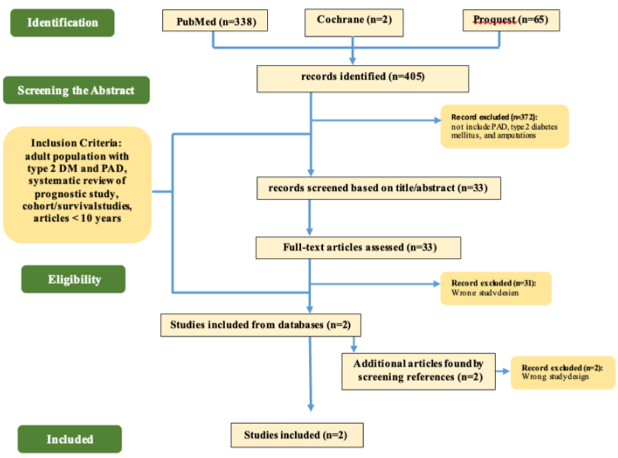

Figure 1. Flowchart of article search results (PRISMA 2020 Flow Diagram)

These articles were considered valid as they met nearly all items on the appraisal checklist. In terms of importance, all two studies were deemed clinically relevant to the patient case discussed in this EBCR, based on their reported incidence and Hazard Ratios (HRs) or Odds Ratio (ORs). All two studies were considered applicable to the patient population in this EBCR, particularly to Indonesian Diabetes Mellitus patients with as a peripheral artery disease.

The first study analyzed 50,276 adults with diabetes (DM) and/or peripheral artery disease (PAD) in West Virginia from 2011–2016 using a large longitudinal electronic health record database. A total of 369 patients (7.3 per 1000) underwent lower- underwent amputation differed markedly from those without amputation. A large majority had both diabetes and peripheral artery disease (DM+PAD) (65.6% vs 18.1%). From a laboratory standpoint, amputation patients had significantly higher HbA1c levels (median 7.3 vs 6.5; p < 0.0001) compared with those without amputation. Multivariable analysis identified PAD and combination of diabetes increased the risk of LEA (aOR 57.76, 95% CI 22.27–149.79) (table 3) (Minc et al., 2021).

The second study analyzed over 118,000 patients undergoing coronary angiography and assessed their 10-year risk of peripheral artery disease (PAD), lower limb revascularization, and amputation, comparing individuals with and without diabetes and coronary artery disease (CAD). Patients with diabetes alone had a higher incidence of PAD (6.9%), lower limb revascularization (1.6%), and amputation (2.4%), corresponding to increase risk of LEA (aHR 3.90, 95% CI 3.55 to 4.28)., respectively (table 3) (Olesen et al., 2021).

Discussion

The clinical question addressed in this Evidence-Based Case Report was whether peripheral artery disease independently predicts lower-extremity amputation in adults with type 2 diabetes mellitus. The evidence synthesized from two cohort studies review consistently demonstrated that PAD is associated with a substantially increased risk of lower-extremity amputation (Minc et al., 2021; Olesen et al., 2021). Although the magnitude of risk varied across studies because of differences in study populations and methodologies, the overall direction of evidence was consistent, indicating that PAD is an important prognostic factor for limb loss in patients with T2DM.

The association between peripheral artery disease (PAD) and lower-extremity amputation (LEA) is supported by well-established pathophysiological mechanisms. In patients with type 2 diabetes mellitus (T2DM), chronic hyperglycaemia promotes endothelial dysfunction through increased oxidative stress, chronic inflammation, and reduced nitric oxide bioavailability, resulting in impaired vascular homeostasis and accelerated atherosclerosis (Boieriu et al., 2025; Hussain, 2025). Diabetes also promotes vascular calcification and diffuse atherosclerotic lesions, particularly in the infrapopliteal arteries, causing progressive arterial narrowing andocclusion. Consequently, blood flow to the lower extremities is markedly reduced, leading to chronic limb ischemia. The coexistence of PAD with diabetic peripheral neuropathy further exacerbates tissue injury, as patients may not recognize minor trauma or ulceration until substantial ischemic damage has occurred. These vascular abnormalities establish a biological basis by which PAD substantially increases the susceptibility of diabetic feet to ulcer progression and limb-threatening complications (Rümenapf et al., 2024).

Chronic ischemia initiates a cascade of pathological events that impair wound healing and ultimately increase the risk of amputation. Reduced tissue perfusion limits the delivery of oxygen, nutrients, growth factors, and circulating immune cells to injured tissues, thereby disrupting each phase of the wound-healing process, including inflammation, angiogenesis, collagen synthesis, and tissue remodeling. Inadequate perfusion also compromises leukocyte migration and function, reducing the host immune response and facilitating persistent bacterial infection. Furthermore, diminished blood supply restricts tissue penetration of systemically administered antibiotics, decreasing treatment efficacy and allowing infection to progress despite appropriate antimicrobial therapy (Riaz et al., 2025). Persistent hypoxia combined with uncontrolled infection promotes progressive tissue necrosis, gangrene, and irreversible limb damage that frequently necessitates lower-extremity amputation (Peng et al., 2025). These biological mechanisms provide a strong pathophysiological rationale for considering PAD an important prognostic factor for LEA in patients with T2DM and support the consistent association observed across the included studies.

Despite differences in effect size, the included studies consistently identified PAD as an important predictor of LEA. Variations in the reported estimates are likely explained by differences in study populations, healthcare systems, definitions of PAD and LEA, duration of follow-up, and statistical adjustment for confounding variables. Therefore, the observed heterogeneity reflects methodological differences rather than conflicting evidence. Overall, the evidence can be considered moderate to high in strength, as it includes two large cohort studies that used multivariable analyses and demonstrated clinically meaningful associations between PAD and amputation.

The progression from diabetic foot ulceration to amputation is multifactorial, and PAD should be interpreted within this broader clinical context. Peripheral neuropathy increases the risk of delayed presentation through loss of protective sensation, while infection may progress to osteomyelitis and systemic sepsis if not promptly treated (Packer et al., 2023). Poor glycaemic control impairs wound healing and immune function, whereas chronic kidney disease contributes to vascular calcification and delayed tissue repair (Sandepudi et al., 2025). Smoking accelerates atherosclerosis and ischemia, and severe ulcers are independently associated with poorer limb outcomes (Wang et al., 2021). Delayed vascular assessment and revascularization further increase the risk of irreversible ischemia and amputation (Chai et al., 2025). Consequently, comprehensive risk assessment should integrate vascular status with neuropathy, infection, metabolic control, renal function, smoking status, ulcer severity, and timely vascular intervention.

The available evidence is directly applicable to the patient described in this report. The patient presented with T2DM, diabetic foot ulceration, intermittent claudication, and clinically confirmed PAD, characteristics comparable to those of participants in the included cohort studies. These findings suggest that the patient is at high risk of LEA and should undergo comprehensive vascular assessment, including pulse examination and ankle–brachial index (ABI) measurement, with toe–brachial index or duplex Doppler ultrasonography when indicated (Tehan et al., 2024). Early referral for vascular consultation and multidisciplinary diabetic foot management is essential to optimize glycaemic control, manage infection, perform revascularization when appropriate, and improve limb preservation.

Although all included studies were conducted outside Indonesia, their findings remain relevant because the underlying pathophysiological mechanisms are universal. However, implementation may vary according to healthcare infrastructure. Tertiary referral hospitals generally have access to ABI measurement, duplex Doppler ultrasonography, vascular imaging, and vascular surgery services, whereas district hospitals and primary healthcare facilities often have more limited diagnostic resources and specialist availability. These findings support current PERKENI recommendations advocating routine foot examination, vascular assessment, optimization of glycaemic control, and multidisciplinary diabetic foot management (Perkeni, 2021). The Indonesian National Health Insurance (JKN) system also provides opportunities to improve access to specialist referral, vascular consultation, hospitalization, wound care, and revascularization. Nevertheless, disparities in healthcare resources, particularly in rural and remote areas, may delay diagnosis and referral, contributing to higher rates of advanced diabetic foot disease and amputation (Maulana et al., 2022). Strengthening primary care capacity, expanding access to vascular services, and improving referral networks should therefore be priorities for limb preservation in Indonesia.

This review has several limitations. Only two eligible studies were included, all conducted in Western populations, limiting generalizability to Asian and Indonesian patients. Considerable heterogeneity existed in study populations, definitions of PAD and LEA, follow-up duration, and adjustment for confounding factors. In addition, the evidence was synthesized narratively because the limited number and heterogeneity of studies precluded meta-analysis. Consequently, although the available evidence consistently supports PAD as an important prognostic factor for LEA, the findings should be interpreted cautiously.

The findings have several important clinical implications. Routine PAD screening should be incorporated into the assessment of patients with T2DM, particularly those presenting with diabetic foot ulcers. Clinical evaluation should include foot examination, peripheral pulse assessment, neuropathy screening using a 10-g monofilament, and objective vascular assessment with ABI, supplemented by TBI or Doppler ultrasonography when indicated. Patients with confirmed PAD should be referred promptly for vascular evaluation to determine the need for endovascular or surgical revascularization. Management should also emphasize optimization of HbA1c, smoking cessation, statin therapy, cardiovascular risk reduction, and multidisciplinary diabetic foot care. These integrated strategies may improve limb preservation and reduce preventable lower-extremity amputations (J. M. Kim et al., 2026).

Future prospective cohort studies involving Asian and Indonesian populations are needed to validate the prognostic value of PAD in diverse healthcare settings. Further research should also develop and externally validate multivariable prediction models incorporating PAD together with other established risk factors and evaluate the effectiveness of early vascular intervention and multidisciplinary diabetic foot care in reducing amputation rates and improving patient outcomes.

Conclusion

The available evidence suggests that peripheral artery disease (PAD) is an important prognostic factor associated with an increased risk of lower-extremity amputation (LEA) in patients with type 2 diabetes mellitus (T2DM). These findings support the incorporation of routine vascular assessment, including ankle–brachial index (ABI) measurement when appropriate, and multidisciplinary diabetic foot management to facilitate early identification of high-risk patients and timely limb-preservation interventions. However, the conclusions should be interpreted cautiously because they are based on a limited number of heterogeneous studies conducted predominantly in Western populations, with no evidence from Indonesia or other Asian countries. Further high-quality prospective studies in diverse populations are needed to validate the prognostic value of PAD and strengthen its applicability to clinical practice, particularly in resource-variable settings.

No	Article Title and Authors	Critical Review Result			
		Validity	Importance	Applicability	Level of Evidence
1.	**Opportunities for diabetes and peripheral artery disease-related lower limb amputation prevention in an Appalachian state: A longitudinal analysis (Minc et al., 2021)**	The study has several strengths that support its internal validity, including a large sample size (>50,000 patients), use of a longitudinal database that captures lab values before and after amputation, clear inclusion criteria, and multivariable regression adjusting for major confounders. Objective identification of amputations using CPT codes also minimizes misclassification. However, the retrospective design introduces potential bias, and the 74% missing laboratory data limits the completeness of analyses. Additional concerns include possible misclassification of DM/PAD severity from ICD codes, underreporting of tobacco use, and the study's restriction to a single tertiary health system, which may not represent the broader population. Overall, internal validity is moderate to high, with limitations typical of retrospective EHR-based studies, yet the associations remain strong and plausible.	The study's findings are highly important due to the exceptionally large effect sizes and clear clinical impact. The combination of diabetes and PAD increased the risk by 57.76 times (95% CI 22.27–149.79), representing a dramatic elevation in vulnerability. Even a 1% rise in HbA1c was associated with a 31% increase in amputation risk, and the observation that CAD was protective by 74% likely reflects the benefits of more intensive medical optimization in these patients. The overall amputation prevalence of 7.3 per 1000 over five years is substantial for a rural population and underscores the urgency of targeted interventions. Overall, the magnitude and	The study's applicability is shaped by its focus on a rural Appalachian population characterized by older age, high tobacco use, low socioeconomic status, and substantial chronic disease burden. These features make the findings particularly relevant to rural and underserved communities but limit generalizability to urban or more affluent settings. Because the data come from a tertiary/quaternary health system with access to vascular specialists, outcomes may differ in regions without comparable resources. Nonetheless, the results hold strong relevance for primary care, endocrinology, vascular surgery, and public health planning, especially in areas with limited access to multidisciplinary limb-salvage services. Overall, external validity is moderate to high for rural and medically underserved populations, but lower for settings with greater healthcare access and resources.	2

			clarity of these associations make the study's findings highly significant and relevant for shaping public health policies and clinical guidelines.		
2.	**Peripheral artery disease, lower limb revascularization, and amputation in diabetes patients with and without coronary artery disease: A cohort study from the Western Denmark Heart Registry (Olesen et al., 2021)**	The study shows strong methodological rigor, supported by its very large sample size (>118,000), use of high-quality Danish national registries, minimal loss to follow-up, and accurate diagnostic coding. The cohort design, exclusion of baseline PAD or amputation, and multivariable Cox regression adjusting for major confounders enhance causal inference, while multiple imputation for missing smoking and BMI data reduces bias. However, as an observational study, it remains vulnerable to residual confounding, particularly because HbA1c and diabetes severity were not captured. PAD may also be underdiagnosed, and reliance on ≥50% stenosis to define CAD could misclassify disease severity. Despite these limitations, the strong and biologically plausible associations reflect moderate to high internal validity**.**	The effect sizes reported are large and clinically meaningful. This study showed that diabetic patients with CAD had increased risk of LEA (aHR 3.90, 95% CI 3.55 to 4.28). The gradients observed by CAD extent, insulin use, and disease duration underscore the cumulative impact of cardiometabolic disease. These findings emphasize that diabetes especially long-standing or insulin-dependent diabetes remains a potent driver of limb loss even with modern cardiovascular therapies. Clinically, this highlights a major unmet need such as traditional CAD risk management does not adequately	The Danish healthcare environment offers strengths for population-level generalizability: universal coverage, robust registries, and standardized care. The findings are highly applicable to high-income countries with similar healthcare structures. However, Denmark's high rates of statin and antiplatelet therapy may result in underestimated absolute risks compared with countries with lower medication access. Because the cohort consisted of patients referred for coronary angiography, applicability to the general population is somewhat limited. Results apply best to patients undergoing cardiac evaluation or those with elevated cardiovascular risk. Nevertheless, the strong, consistent effects of diabetes across subgroups suggest broad relevance to global diabetes populations. Overall, applicability is moderate to high for most clinical settings, though lower for low-resource environments where screening, medication access, and	2

	prevent PAD or amputation in diabetes. The differentiation between distal amputations (more common in diabetes) and proximal amputations (more common with CAD) also provides insight into mechanisms and potential prevention strategies. Overall, the outcomes are robust and have substantial implications for clinical practice, guideline development, and public health planning indicating very high importance.	revascularization services differ substantially.

Early identification of peripheral artery disease through routine foot examinations and appropriate vascular assessment, combined with optimization of glycaemic and cardiovascular risk factors, is essential to reduce the risk of lower-extremity amputation in patients with type 2 diabetes mellitus. Timely referral to multidisciplinary diabetic foot teams can facilitate comprehensive management of ischemia, infection, and wound care, while patient education on foot self-care and early recognition of symptoms may further improve outcomes. At the health-system level, strengthening standardized diagnostic pathways, surveillance systems, and access to vascular services, particularly for rural and other high-risk populations, together with further research to validate effective limb-preservation strategies, is needed to improve diabetes-related foot care.

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