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Clinical Decision Support for Peripheral Artery Disease: Answering the Call

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Approximately 1 in 20 or ≈8.5 million Americans in the United States have peripheral artery disease (PAD).[1] Of these, many are asymptomatic or have mild symptoms, whereas a smaller group experiences the more advanced form, critical limb ischemia (CLI). Clearly, PAD is associated with significant morbidity and mortality and has been recognized as a coronary artery disease risk equivalent. Yet, a lot more work remains to improve our care of patients with PAD, including to ensure regularly prescribing the proven, guideline-driven therapies that have been demonstrated to be effective but are often not routinely implemented. What will make us better at prescribing proven therapies we often ignore? Do we need more electronic alerts? Or more clinical calculators? PAD is common among patients with coronary artery disease, chronic kidney disease, and diabetes mellitus, and many predictive models and calculators have already been created for these conditions. Will adding yet another calculation of a predictive outcome to the clinical visit for this vulnerable patient population improve our care? Ultimately, if stacking calculators atop predictions atop alternate clinical decision support (CDS) tools is the path to clinical efficacy, what steps can we take to help improve how multiple different clinical models interact and how can we help clinicians use them effectively and efficiently?

In this issue of the *Journal of the American Heart Association* (*JAHA*), Arruda-Olson et al report on their creation of a real-time risk calculator for patients with PAD and deployment of this calculator at the point of care.[2] A study cohort of 1676 subjects was used to develop a Cox model for 5-year mortality, assessing multiple risk factors. The model parameters were used to derive a formula for calculation of individual risk and for deployment of this calculator via the electronic health record.

Clinical variation in successful prescription of goal-directed medical therapy in patients with PAD is well documented. A recent report from the Veterans Affairs health system demonstrated that, despite guideline recommendations for statin therapy in PAD, only 41% of all patients with PAD were prescribed statins.[3] Recent analysis by Hess et al[4] demonstrated similar failures in goal-directed medical therapy *even when* patients with PAD had a "capture event," such a clinical revascularization treatment. In these patients discharged after a revascularization procedure, only 61.7% were treated with statin therapy at the time of discharge. Only 67.3% of these patients were discharged on aspirin, and only 57.5% were discharged on a P2Y12 inhibitor.[4] These percentages were low despite the patients in this analysis clearly having *recognized* PAD of above average severity. A general population of patients with PAD likely has even poorer implementation of guideline-recommended therapies. These failures have led many in the community to call for improved implementation of CDS tools *at the point of care*.[5]

Arruda-Olson et al[2] should be applauded for their work taking on this challenge. PAD is not the easiest of clinical conditions to identify from searchable electronic health record variables, and the authors were meticulous in their development of the data set from which their risk calculator was built. Rather than deriving their calculator from a population with PAD with disease documented on simple vascular laboratory evaluation (a subset of the entire population with PAD), they derived their calculator from a population with PAD identified via use of a previously reported billing code algorithm.[6] This makes their resultant calculator significantly more applicable to patients seen in a community care setting (the patients to benefit from potential CDS tool implementation). The authors derived their calculator to predict *mortality* but not hospitalization, major adverse cardiovascular events, or major adverse limb events. Predicting mortality *may* allow the calculator to influence prescription patterns of clinicians and adherence patterns of patients because of the severity of the predicted risk. However, the ability to predict other outcomes

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in this patient population is also extremely important. Indeed, the complexity of clinical management of PAD has led to some therapies improving mortality while potentially increasing the risk of major amputation.[7] The dramatic association in patients with CLI of amputation with impending mortality also demonstrates the importance of being able to predict major adverse limb events as an intermediate predictor.[8]

The work presented herein is not without limitations. To begin, the generalizability of the risk calculator is limited by the derivation cohort that included 94% non-Hispanic whites from a single county in Minnesota. Generalizability of risk predictions may thus be limited in patients not matching the derivation cohort. Furthermore, the varying categories of PAD, ranging from asymptomatic PAD to CLI, may limit success of the calculator across clinical conditions. The natural history of CLI is different from that of PAD in general, with nearly 25% of patients presenting with CLI experiencing cardiovascular death *within 1 year* of diagnosis.[9] The ability to predict mortality in patients with CLI from a calculator derived from patients with general PAD (24% with CLI) may be limited by comparison to a CLI risk calculator derived from an exclusive population with CLI.

Another caveat to applicability of this tool comes from the finding that in this derivation cohort, aspirin did not have a demonstrated protective effect. Multiple trials and consensus statements have supported implementation of aspirin monotherapy in patients with PAD.[10,11] That a cohort derived to be representative of all patients with PAD does not demonstrate the protective effects of aspirin should raise questions about the development of the model and the utility of its prediction.

CDS tools have demonstrated significant successes in tasks, including performing preventative services, ordering appropriate clinical studies, and prescribing clinical therapies.[12] Nonetheless, the implementation of any CDS tool faces certain challenges to which this PAD prognostic tool is not immune. CDS recommendations must be prioritized and filtered. Would a PAD CDS calculator provide a risk class and concurrent recommendation for *every patient* seen in a primary care setting? If so, should this calculator be prioritized over a cardiovascular risk calculator? A chronic kidney disease progression risk calculator? Where does it stop? Alarm fatigue is a real phenomenon, and its potential for precipitation of medical errors in all clinical settings has been robustly described.[13] Rigidity of CDS systems is another frequently cited concern in the field. Do clinicians reliant on a PAD tool neglect to evaluate and treat PAD in patients not identified by an imperfect tool?

Our diagnostic and therapeutic modalities can only be as good as our ability to recognize the patients in whom they should be implemented. And continuing medical education, association outreach, disease advocacy, and various permutations of provider education can all go only so far in terms of optimizing our recognition of disease. In a world in which portable devices alert us incessantly of our obligations and opportunities outside of clinical care, it is not surprising that we turn to technology to attempt to similarly improve our identification and treatment of disease. But the specificity of CDS tools like that presented herein often raises concerns because rather than providing a complete overhaul of our recognition and treatment of disease, the tool represents simply a small part of a huge whole. Imagine a new alert system on a cellular telephone that would recognize and prioritize a subset of your business calls. Would this system make you more likely to ignore other business calls from outside of the subset? Would it make you less likely to respond to telephone calls from family? Would it even make you better at recognizing the calls it was supposed to highlight? Or would it just make you deem your cellphone a more annoying tool in general than you already believed it to be? Although a reliable CDS calculator can be developed, these same questions can be raised about its utility in implementation at point of care and its impact on PAD care as well as on clinical care outside of PAD. The authors reported creation of the tool. They did not demonstrate clinical effectiveness of implementation of the tool. Per their discussion, a prospective quality project evaluating the impact of their CDS tool is ongoing currently. It will be exciting to see in the future if implementation of their robust calculator actually affects clinician adherence to guidelines or even clinical outcomes in PAD.

Despite specific and CDS-field limitations, the work presented herein is valuable because it represents a large step forward in multiple long journeys. It is essential to have built a tool that identifies and risk stratifies a disease that is generally underrecognized and undertreated. It is important to step boldly into creation of CDS tools and to tackle the power of complex informatics within our electronic health record, despite the technical and systems-level concerns that exist for CDS in general. Bigger questions do remain. How do we organize large multicenter data sets from which future similar calculators with more broad applicability can be derived? As CDS for more conditions and therapy implementations come online, how do we control and improve the user interface that allows interaction between the tools and between the end user and the tools?

Novel methods, including machine learning and neural networks, also offer ever-increasing opportunities for prediction and automation of clinical tasks. Rather than the present in which clinicians are prompted at the point of care to recognize and respond to distinct calculator predictions, imagine a future in which machine learning models trained on clinical data sets deemed medically optimized would make diagnostic and therapeutic recommendations for practitioners

to accept or refuse, driven not by a single *International Classification of Diseases, Tenth Revision* (*ICD-10*) code, but by complex combinations of demographic, socioeconomic, and clinical factors. In this future, we will not have distinct calculators categorizing a single condition, but we will have machine algorithms "treating the whole patient" the same way we strive to as physicians. And imagine these methods getting better every time we use them, learning from their success, from their failure, and from clinician refusals the same way our dictation software improves its ability to recognize our speech every time we dictate a discharge summary. In this not-too-distant future, "standard of care" may represent evaluation of patients by machine learning algorithms and clinician assessment of that evaluation. In this world, neural networks trained on medically optimized cases could make recommendations not driven solely by variables inputted into a calculator, but by image analysis of wounds or by risk optimization strategies we may have never conceived but that were hypothesized by unsupervised machine learning data analysis. None of this is science fiction anymore. We really do stand at the cliff's edge of revolutionizing our clinical systems and processes with novel tools. We should all be thankful that the calls we have all made for so long for methods to improve our processes are being heard and acted on.

Disclosures

None.

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