

# Can blood protein levels predict outcome in peripheral arterial disease?

## What is the problem?

Peripheral arterial disease (PAD) is a common disease which results in hardening and narrowing of blood vessels, mainly in the leg. Patients with PAD complain of pain in their legs when they exercise due to a lack of blood and oxygen, which leads to the build-up of lactic acid in the muscles.

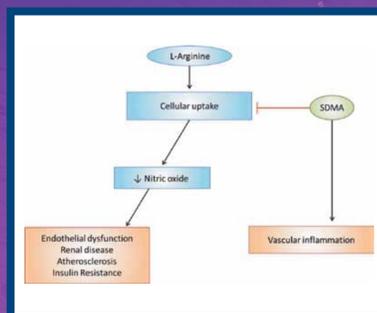


Figure 1: The role of SDMA in nitric oxide production.

One of the reasons for the arteries becoming diseased is that the inner blood vessel lining (endothelium) in these patients does not produce enough of a substance called nitric oxide, which helps control blood flow and blood pressure. The concentration of nitric oxide is reduced by proteins called dimethyl-arginines, one of these is known as symmetric dimethyl-arginine (SDMA) which is an inhibitor of nitric oxide production.

## How serious is it?

Peripheral Arterial Disease is estimated to affect up to 12% of people aged between 55 and 70 years, rising to even 20% in older individuals. As well as having difficulty walking, patients with this condition are also much more likely to die of a heart attack or stroke.

## How has our research helped to solve it?

In our study we have shown for the first time that there is a relationship between the levels of SDMA, an inhibitor of nitric oxide, and the survival of a patient with peripheral arterial disease. Patients with high levels of this inhibitor were more likely to die.

Future studies will look at patients with high levels of SDMA to see if certain drugs can protect the blood vessels.

## What did we do?

We aimed to assess if there was any relationship between levels of SDMA and: (1) how severe the patient's peripheral arterial disease was and; (2) patient survival.

1. Blood samples were taken from 238 patients with peripheral arterial disease who attended the vascular clinic at Aberdeen Royal Infirmary between 2004 and 2006.
2. Levels of SDMA were measured by a technique known as High Pressure Liquid Chromatography – Tandem Mass spectrometry.
3. We performed statistical tests to see if levels were higher in those patients who: (1) had more severe disease and also (2) those who had died approximately 7 years after the blood sample was taken, compared with those patients who were still alive. The Scottish National Health Service intranet system was used to establish mortality in patients.

## What did we find?

1. SDMA levels were higher in those who died compared with those who were alive.

	Total Cohort N=238	Alive N=138	Dead N=99	p value
SDMA ( $\mu\text{mol/L}$ )	0.48 (0.40-0.61)	0.46 (0.39-0.55)	0.51 (0.44-0.66)	<0.001
Quartile				
1 <sup>st</sup> (<0.40)	59 (25%)	44 (32%)	15 (15%)	0.001
2 <sup>nd</sup> (0.40-0.48)	59 (25%)	34 (25%)	24 (24%)	
3 <sup>rd</sup> (0.49-0.61)	61 (26%)	37 (27%)	24 (24%)	
4 <sup>th</sup> ( $\geq 0.62$ )	59 (25%)	23 (17%)	36 (36%)	

Table 1: SDMA levels.

2. Levels of SDMA, as continuous variable, were significantly associated with mortality ( $p < 0.001$ ).

3. Patients with the highest SDMA levels (highest quartile) were more likely to die than those with the lowest (lowest quartile). (SDMA Hazard ratio = 3.855, 95% CI 1.625 - 9.143,  $p = 0.002$ ).

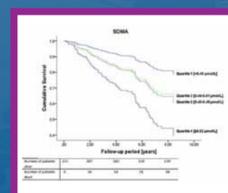


Figure 2: Survival curve.

Patients whose levels of SDMA were above  $0.62 \mu\text{mol/L}$  (purple line) were nearly 4 times more likely to die when compared with those whose levels were below  $0.40 \mu\text{mol/L}$  (blue line).

4. Higher levels of SDMA were associated with increasing severity of PAD ( $r = -0.209$ ,  $N = 208$ ,  $p = 0.002$ ).

Levels ( $\mu\text{mol/L}$ )	Severe artery disease (ABI <0.5)	Less severe artery disease (ABI >0.5)	p value
SDMA	0.51 (0.43-0.64)	0.46 (0.39-0.55)	0.010

Table 2: ABI - ankle brachial index and SDMA levels. ABI measured by dividing blood pressure at ankle with blood pressure at brachial artery in the arm (see interactive display).

## Who am I?

I am a medical student at the University of Aberdeen. I did this project during my summer holidays. I enjoyed my research so much that I am now doing an intercalated degree in medical science, and then will continue my medical studies, aiming to graduate and become a doctor in August 2017. In the longer term, I want to become a surgeon specialising in treating patients with arterial disease, and to be active in research (an academic vascular surgeon).

## What does it mean?

Our findings show that in patients with peripheral arterial disease, levels of symmetrical dimethyl-arginine may help to predict a patient's outcome and may be a future target for drug treatment.

## Acknowledgements

This study was supported by a grant from Medical Research Scotland and the Scottish Chief Scientist Office.

The results of this study have been accepted for publication: Staniszewska, A., Rajagopalan, S., Al-Shaheen, A., Thies, F. & Brittenden, J. (in press). Increased levels of symmetrical dimethyl-arginine are associated with all-cause mortality in patients with symptomatic peripheral arterial disease. *Journal of Vascular Surgery*.