AGE Reader

Clinical cases

Europe

Diagnoptics

4 clinical cases

1. Prediction of neuropathy in type 2 diabetes patients
2. Prediction of nephropathy in type 2 diabetes patients
3. Prediction of cardiovascular complications in type 2 diabetes patients
4. Prediction of cardiovascular events (and amputations) in atherosclerosis patients

1. Diabetic neuropathy

AGE Reader as a predictor of neuropathy in type 2 diabetes

Diagnoptics

1. Diabetic neuropathy

- Current situation:
  - Early detection of neuropathy at the subclinical stage is important to slow or stabilize the sensory deficit and to provide education for the prevention of foot ulcers.
  - Diabetic neuropathy usually diagnosed only when symptoms have arrised (too late).
  - Diagnostics tests used in clinical practice:
    - Complete foot exam once a year
    - Filament test: sensitivity to touch
    - EMG: nerve conduction (not in primary care)

- Adding the AGE Reader measurements to the screening for diabetic neuropathy will lead to:
  - Early detection of (risk of) diabetic neuropathy → selection of patients for additional diagnostics tests.
  - Prevention of diabetic neuropathy in an early stage
  - Higher patient participation grade for diagnostics because of the 12 seconds non-invasive test.

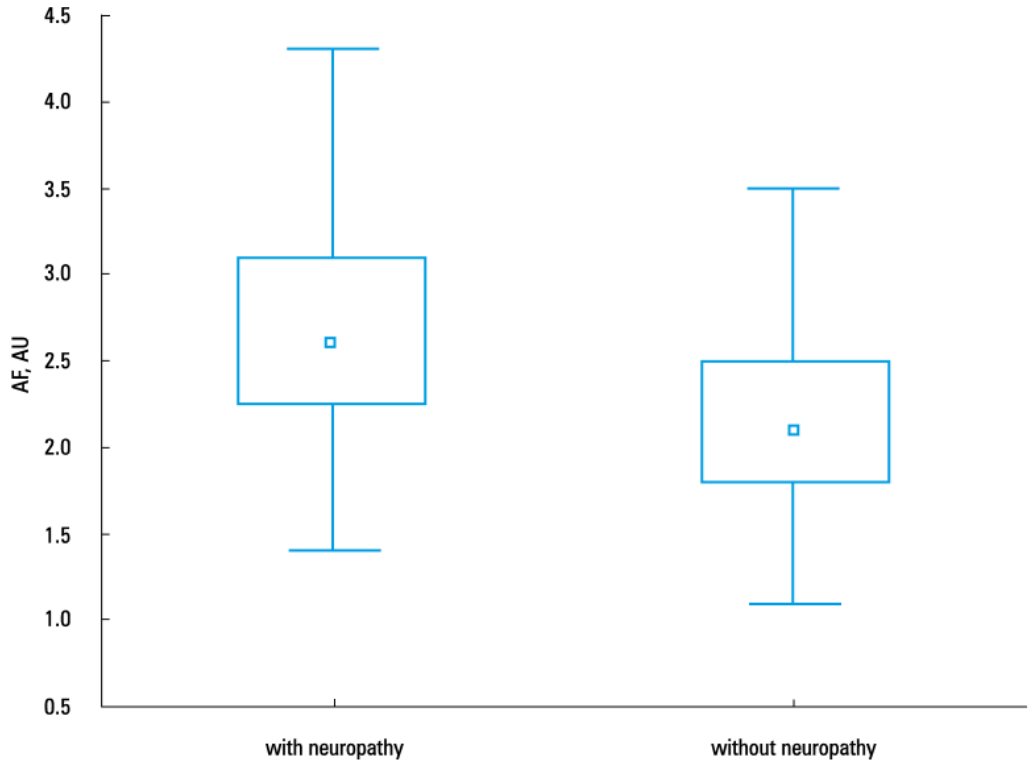
1. Diabetic neuropathy

Supporting studies in scientific literature

1. Diabetic neuropathy

- Araskiewicz 2016

FIGURE 1 Skin autofluorescence in type 1 diabetes patients with and without diabetic peripheral neuropathy



Diagnoptics

1. Diabetic neuropathy

- Araskiewicz 2016

TABLE 3 Variables associated with the presence of diabetic peripheral neuropathy in multivariate logistic regression

Independent variable	DPN	
	P value	odds ratio (95% confidence interval)
male sex	0.93	0.96 (0.46–2.03)
age	<0.001	1.09 (1.05–1.14)
diabetes duration	0.51	0.98 (0.93–1.03)
smoking	0.70	0.84 (0.35–2.04)
skin AF	<0.001	4.16 (1.88–9.20)

Male sex, age, diabetes duration, smoking, and skin AF as independent variables

1. Diabetic neuropathy

- Rajaobelina 2017 (Bordeaux)

Table 4. Neurological tests at 4-year follow-up according to baseline quartiles of sAF

Quartiles of sAF	VPT (V), mean (SD) $n = 132$	DN4 score ≥1, n (%) $n = 132$	Muscle strength (kg), mean (SD) $n = 132$	Feet ESC (μS), mean (SD) $n = 100$
≤1.75	8.2 (8.0)	11 (33.3)	36.0 (13.3)	75.2 (10.9)
]1.75–2.00]	7.6 (6.2)	14 (37.8)	32.8 (11.9)	72.7 (12.4)
]2.00–2.40]	11.1 (9.5)	7 (23.3)	30.1 (11.1)	80.7 (6.1)
>2.40	19.0 (12.7)	19 (59.4)	25.6 (10.3)	68.1 (15.9)
P values				
Global[a]	<0.0001	0.03	<0.0001	0.006
Highest *versus* the others[b]	0.0001	0.006	0.002	0.03

Abbreviations: DN4, Douleur neuropathique en 4 questions; ESC, electrochimical skin conductance; VPT, vibration perception threshold.
[a]ANOVA was performed for continuous variables with log transformation for VPT and Fisher test for DN4 score (categorical variable).
[b]Student test was performed for continuous variables with log transformation for VPT and $\chi 2$ test for DN4 score.

Conclusions: In our patients with T1DM, a high skin AF(>2.4) was associated with a higher risk of signs of neuropathy 4 years later.

1. Diabetic neuropathy

- Gerrits 2008:
  - 657 patients without neuropathy on day 1
  - After follow-up of 3 years the following percentages devloped neuropathy:

Table 4—*Prediction of newly developed microvascular complications subdivided into three skin autofluorescence (AF) groups*

Microvascular complication	*n**	Skin AF <2.35 AU	2.35 ≤ Skin AF <3.00 AU	Skin AF ≥3.00 AU
Retinopathy	708	15/241 (6.2)	18/251 (7.2)	28/216 (13.0)
Neuropathy	662	11/219 (5.0)	27/247 (10.9)	28/196 (14.3)
(Micro)albuminuria	657	18/225 (8.0)	31/253 (12.3)	38/179 (21.2)
Any	431	23/161 (14.3)	41/167 (24.6)	45/103 (43.7)

Data are *n* (%) of newly developed microvascular complications of subgroups compared with the group who did not develop a microvascular complication. *Patients who did not have a complication at baseline. Subgroups of skin AF are tertiles rounded to a practical level.

  - **Conclusion:** Skin AF of >2.35 leads to 2,5 fold increase in risk of developing neuropathy.

Diagnoptics

2. Diabetic nephropathy

AGE Reader as a predictor of nephropathy in type 2 diabetes

2. Diabetic nephropathy

- Current situation:
  - Diagnostics tests used in clinical practice:
    - Urine test: microalbuminuria
    - Blood test: creatinine
    - eGFR calculation

- Adding the AGE Reader measurements to the screening will lead to:
  - Early detection of (risk of) diabetic nephropathy
  - Prevention of diabetic nepropathy in an early stage
  - Higher patient participation grade for diagnostics because of the 12 seconds non-invasive test.

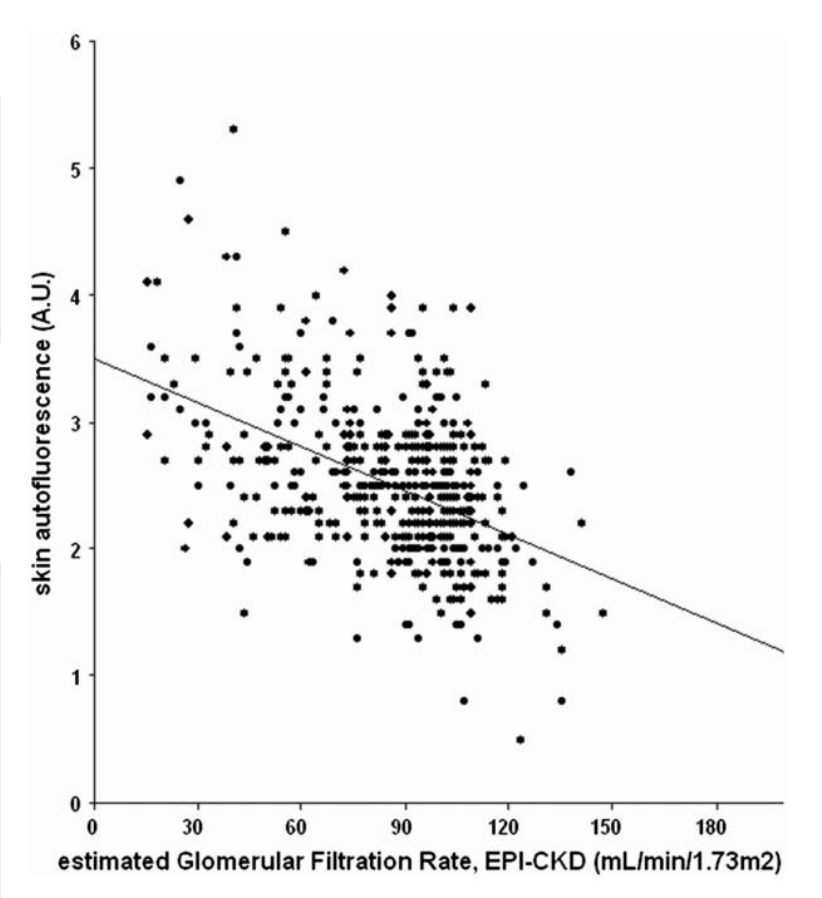
Diagnoptics

2. Diabetic nephropathy

Supporting studies in scientific literature

2. Diabetic nephropathy

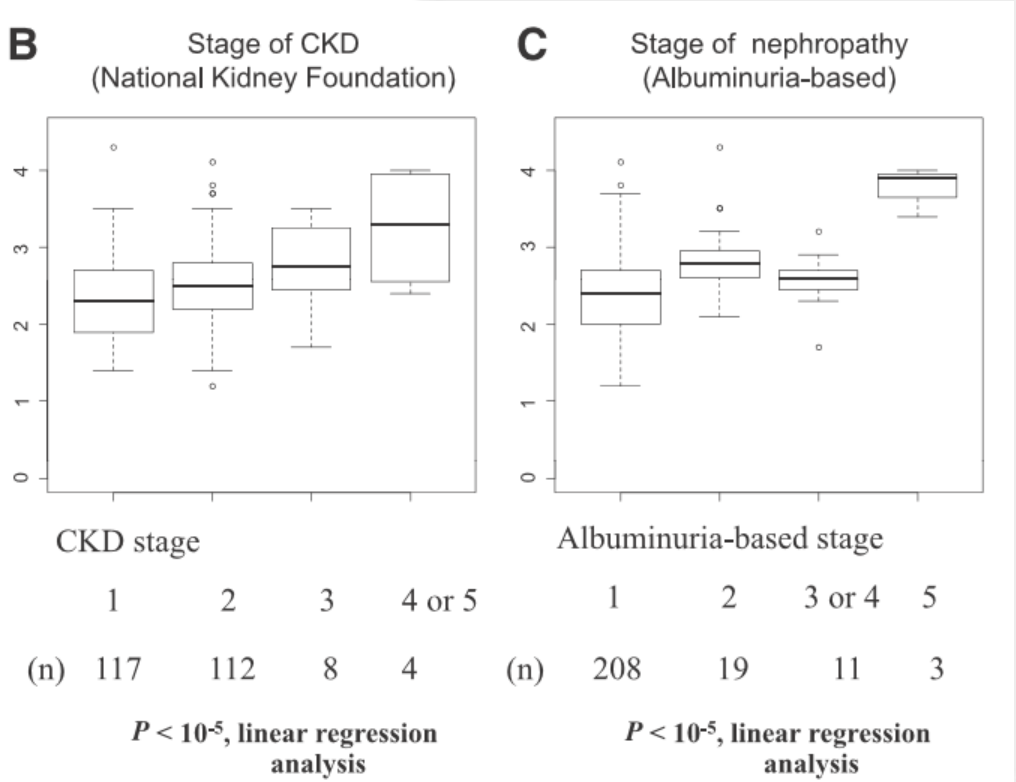
Rigalleau 2014:



Accumulation of AGEs is independently associated with renal insufficiency (and macroangiopathy) in patients with T2D

2. Diabetic nephropathy

Sugisawa 2013



Only skin AF was the significant variable associated with the albuminuria-based stage of nephropathy.

2. Diabetic nephropathy

- Gerrits 2008:
  - 657 patients without (micro)albuminuria on day 1
  - After follow-up of 3 years the following percentages devloped (micro)albuminiria

Table 4—*Prediction of newly developed microvascular complications subdivided into three skin autofluorescence (AF) groups*

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Data are *n* (%) of newly developed microvascular complications of subgroups compared with the group who did not develop a microvascular complication. *Patients who did not have a complication at baseline. Subgroups of skin AF are tertiles rounded to a practical level.

  - **Conclusion:** Skin AF of >2.35 leads to 2 fold increase in risk of developing (micro)albuminuria.

Diagnoptics

3. Diabetes CV complications

AGE Reader as a predictor of cardiovascular complications in type 2 diabetes

3. Diabetes CV complications

- Current situation:
  - Assessment of cardiovascular risk based on classic risk factors.
  - Use of risk scores for predicting risk of cardiovascular events: ProCam and SCORE.

- Adding the AGE Reader measurements to the routine check-ups will lead to:
  - Better cardiovascular risk prediction
  - Personalized risk assessment (tailor made in stead of 1 size fits all)
  - Clinically relevant extra information for clinical decision making
  - Improved patient motivation and treatment adherence

3. Diabetes CV complications

Supporting studies in scientific literature

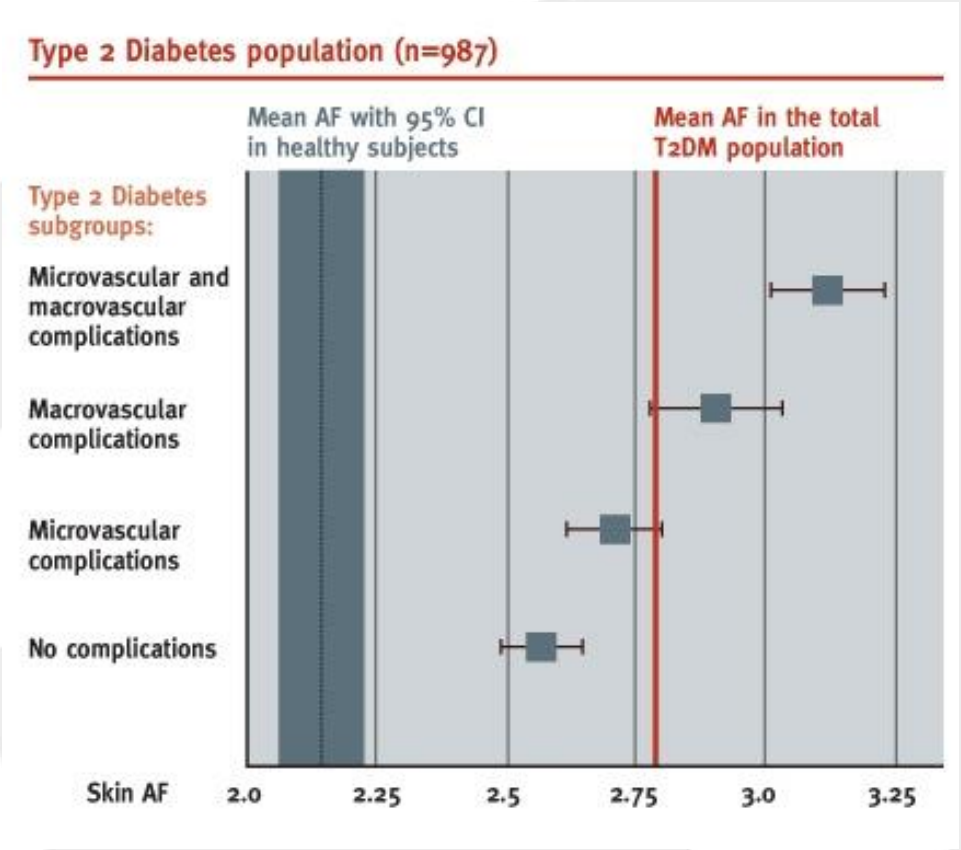
3. Diabetes CV complications

Cross-sectional study complications

Non-invasive AGE-measurements by skin autofluorescence in patients with Type 2 Diabetes Mellitus. Tool for risk-assessment of diabetes complications?

Lutgers H, et al. Diabetes Care. 2006 Dec;29(12):2654-9

3. Diabetes CV complications



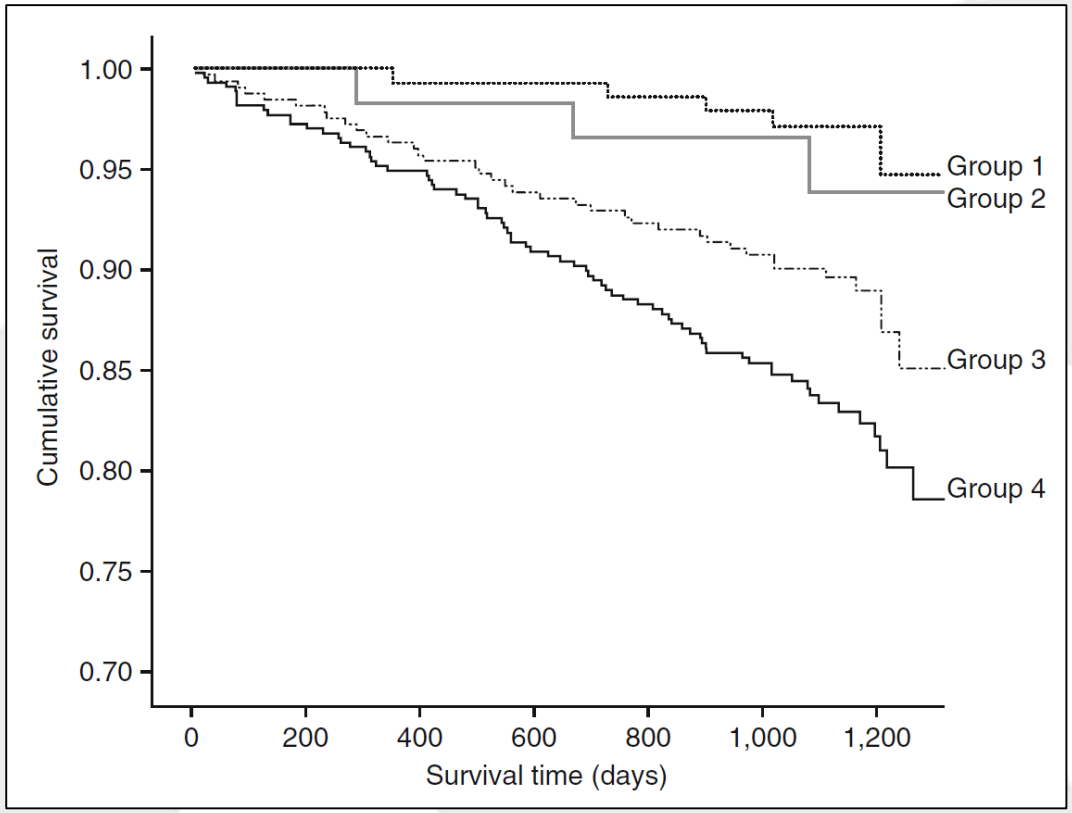
Conclusion: AGE Reader (Skin AF) measurement is elevated in diabetes and reflects the level of vascular damage in diabetes patients.

3. Diabetes CV complications

Prospective study cardiovascular complications and UKPDS

Skin autofluorescence provides additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in type 2 diabetes mellitus.
Lutgers H. et al, Diabetologia, 2009; 52(5): 789-797

3. Diabetes CV complications



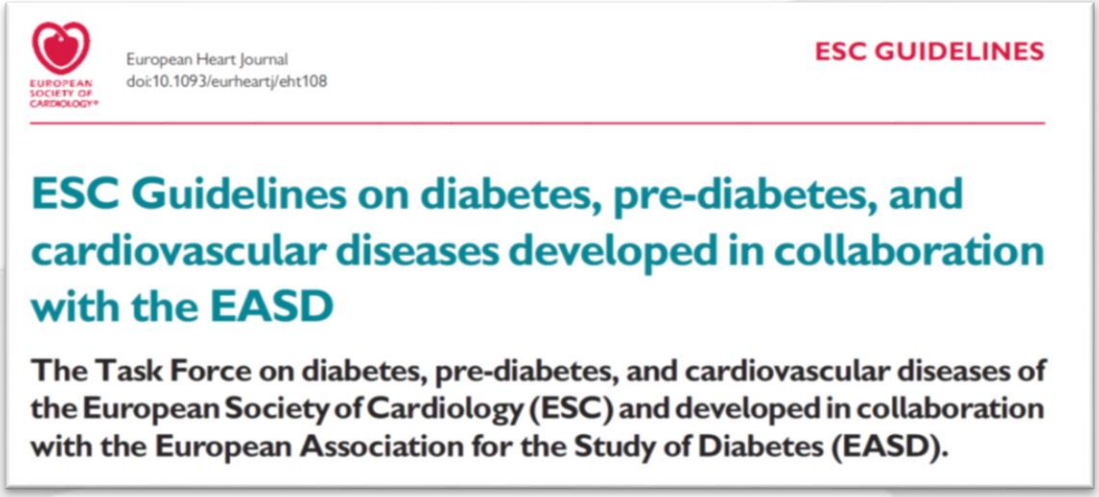
1. UKPDS < median & AF < median
2. UKPDS < median & AF > median
3. UKPDS > median & AF < median
4. UKPDS > median & AF > median

1. AGE Reader measurement is best single predictor of cardiovascular mortality, except age.
2. When compared to UKPDS risk engine:
   - Indenpendent predictor
   - 27% re-classification

3. Diabetes CV complications

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD:

3. Diabetes CV complications



European Heart Journal
doi:10.1093/eurheartj/eht108

ESC GUIDELINES

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD).

A Dutch study involving 972 DM patients evaluated baseline UKPDS risk score and the accumulation of advanced glycation end-products (AGEs) in skin[111] using auto-fluorescence. The addition of skin AGEs to the UKPDS risk engine resulted in re-classification of 27% of the patients from the low- to the high-risk group. The 10-year cardiovascular event rate was higher in patients with a UKPDS score >10% when skin AGEs were above the median (56 vs. 39%).[112] This technique may become a useful tool in risk stratification in DM but further information is needed for this to be verified.

3. Diabetes CV complications

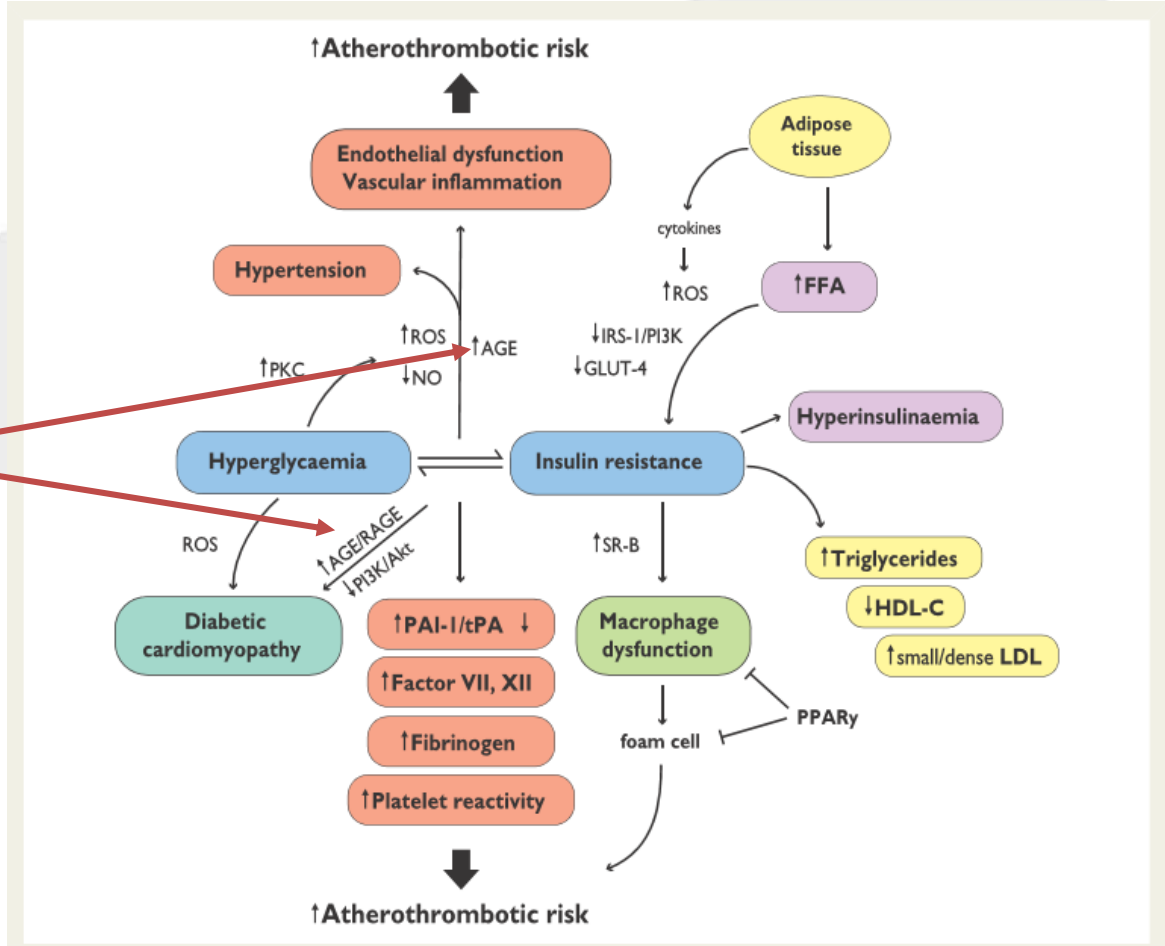


Figure 6 Hyperglycaemia, insulin resistance, and cardiovascular disease. AGE = advanced glycated end-products; FFA = free fatty acids; GLUT-4 = glucose transporter 4; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein particles; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; PKC = protein kinase C; PPARγ = peroxisome proliferator-activated receptor γ; PI3K = phosphatidylinositide 3-kinase; RAGE = AGE receptor; ROS = reactive oxygen species; SR-B = scavenger receptor B; tPA = tissue plasminogen activator.

3. Diabetes CV complications

User reference (attachment):

Messung der Autofluoreszenz der Haut mit dem AGE Reader

Dr. med. Ovidiu Alin Stirban Leitender Arzt des Bereichs Diabetologie und Endokrinologie, Sana Klinikum Remscheid und MVZ Sana Arztpraxen Remscheid.

4. Atherosclerosis

AGE Reader as a predictor of CV events and amputations in atherosclerosis

4. Atherosclerosis

- Current situation:
  - Diagnostics tests used in clinical practice:
    - Framingham and SCORE risk scores
  - Risk scores not suited for secondary cardiovascular prevention in atherosclerosis patients
  - Classic risk factors in these risk scores are often modified by medication.

- Adding the AGE Reader measurements to patient monitoring will lead to:
  - Early detection of risk of cardiovascular events and amputation
  - Patient stratification for secondary cardiovascular prevention
  - Clinicaly relevant information that helps in decision making about interventions

4. Atherosclerosis

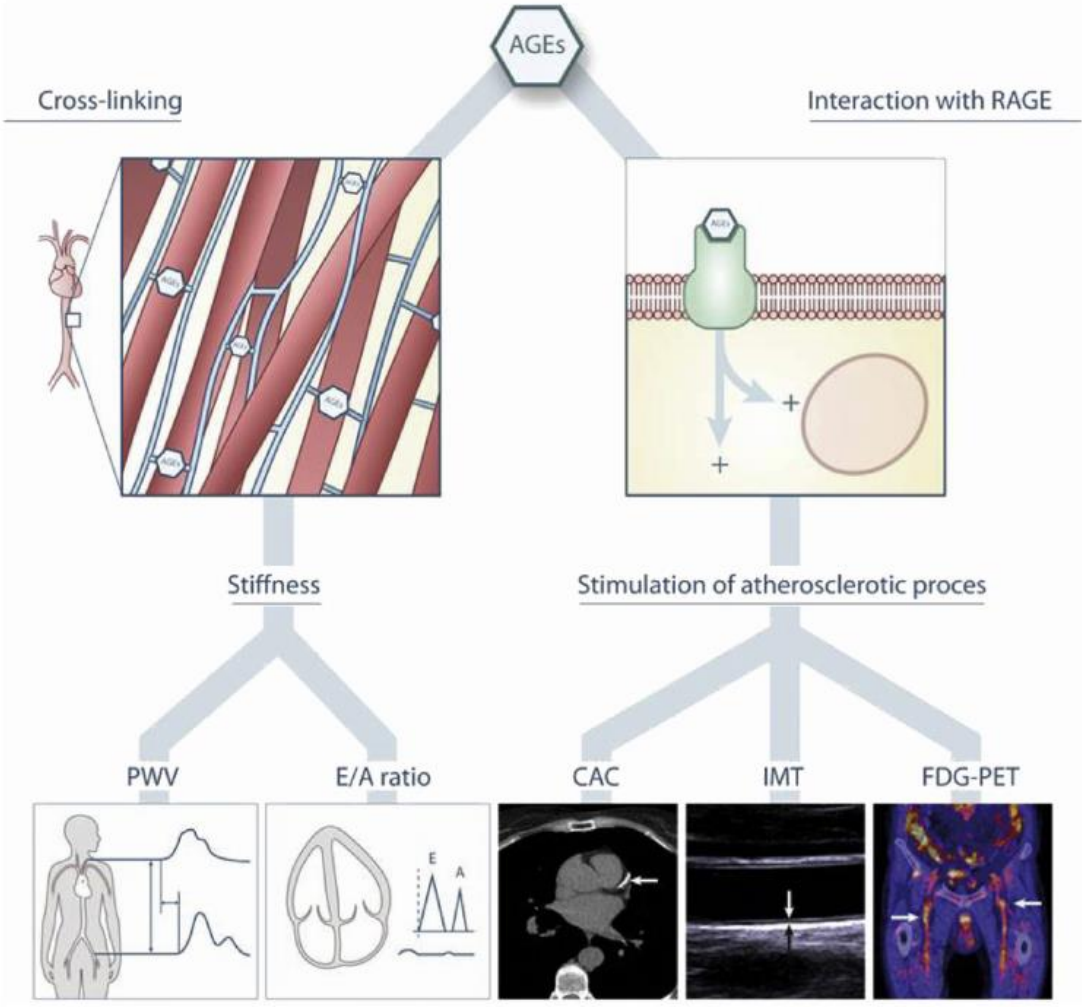
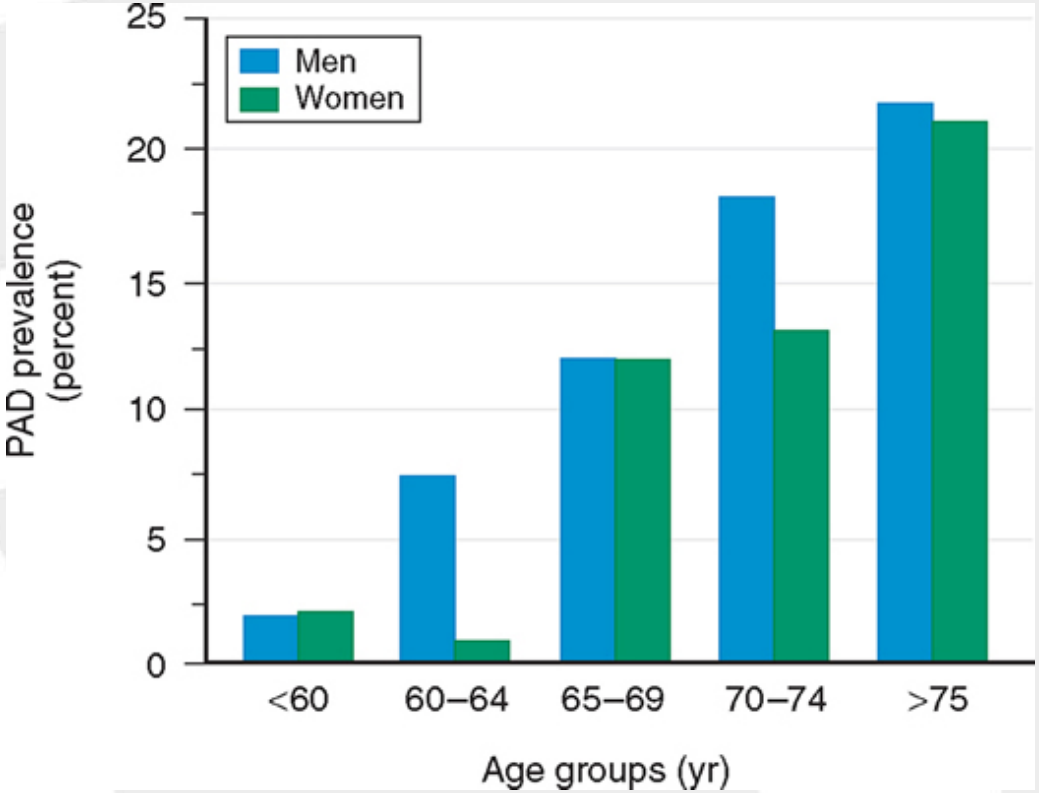


Fig. 3. Vascular effects of advanced glycation end products (AGEs). CAC, coronary artery calcium; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; IMT, intima-media thickness; PWV; pulse wave velocity; RAGE, receptor for advanced glycation end products.

4. Atherosclerosis

- Prevalence Peripheral Artery Disease in USA:



4. Atherosclerosis

Supporting studies in scientific literature

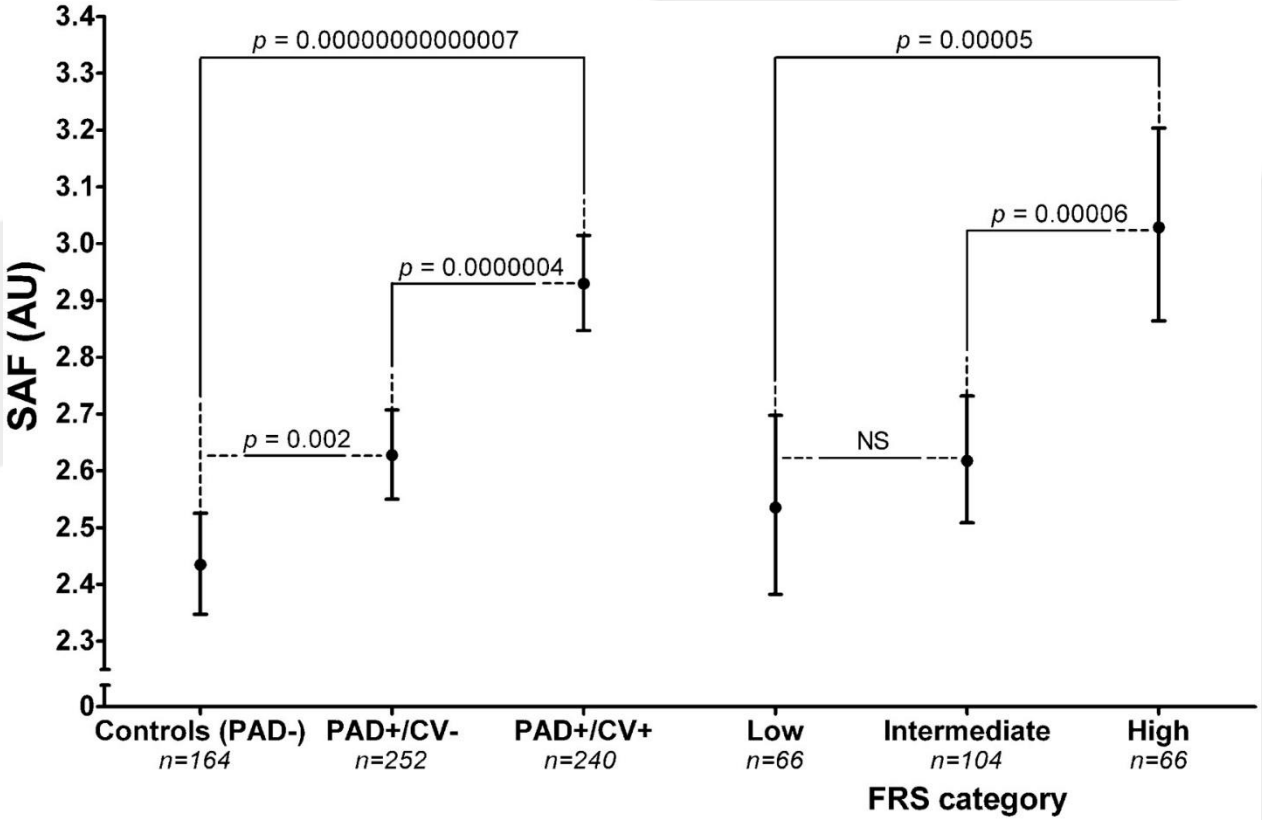
4. Atherosclerosis

Cross-sectional study peripheral artery disease

Skin autofluorescence as a measure of advanced glycation end products deposition is elevated in peripheral artery disease.

de Vos LC. et al. Arterioscler Thromb Vasc Biol. 2012

4. Atherosclerosis



Conclusion: AGE Reader measurement is increased in patients with peripheral artery disease (and cardiovascular disease) and is associated with the Framingham Risk Scores.

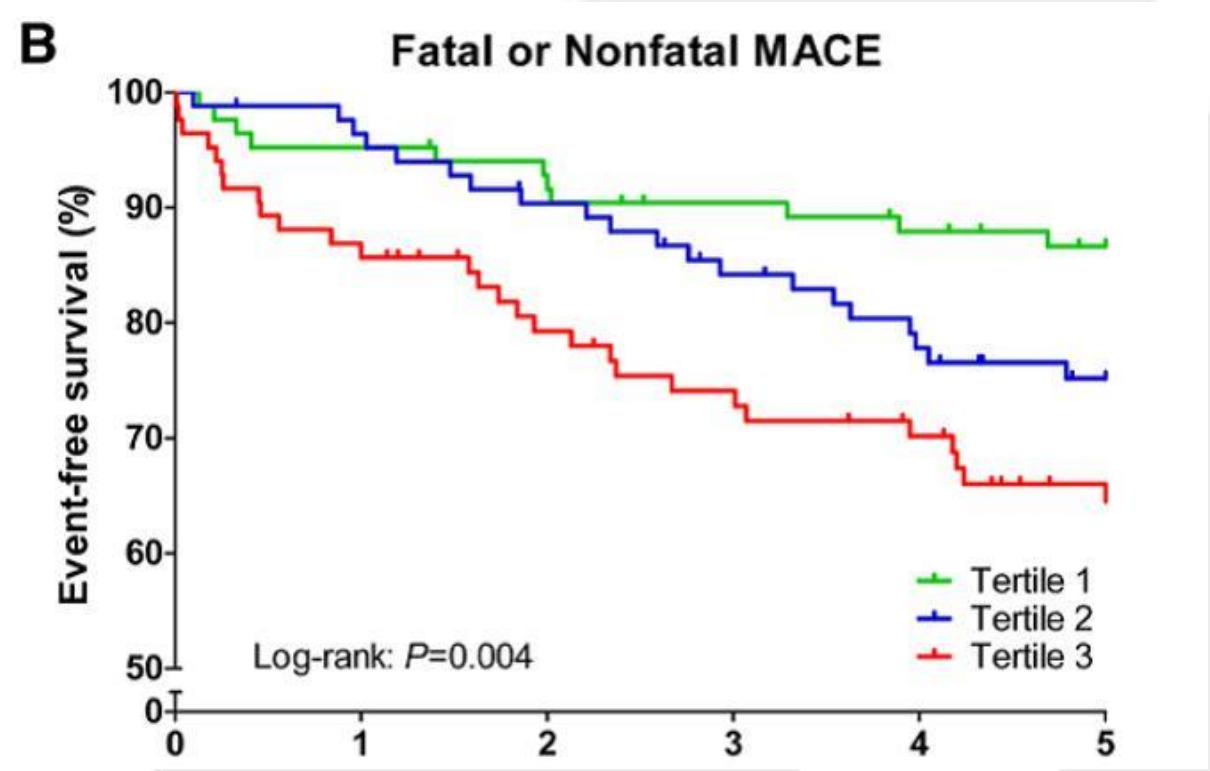
4. Atherosclerosis

Prospective study peripheral artery disease – cv events

Skin Autofluorescence Is Associated With 5-Year Mortality and Cardiovascular Events in Patients With Peripheral Artery Disease.

de Vos LC. et al. Arterioscler Thromb Vasc Biol. 2014 Feb 13.

4. Atherosclerosis



Conclusion: AGE Reader measurement is independently associated with all-cause mortality and fatal or nonfatal MACE (Major Adverse Cardiovascular Events) in patients with peripheral artery disease after a 5-year follow-up

4. Atherosclerosis

Prospective study peripheral artery disease - amputations

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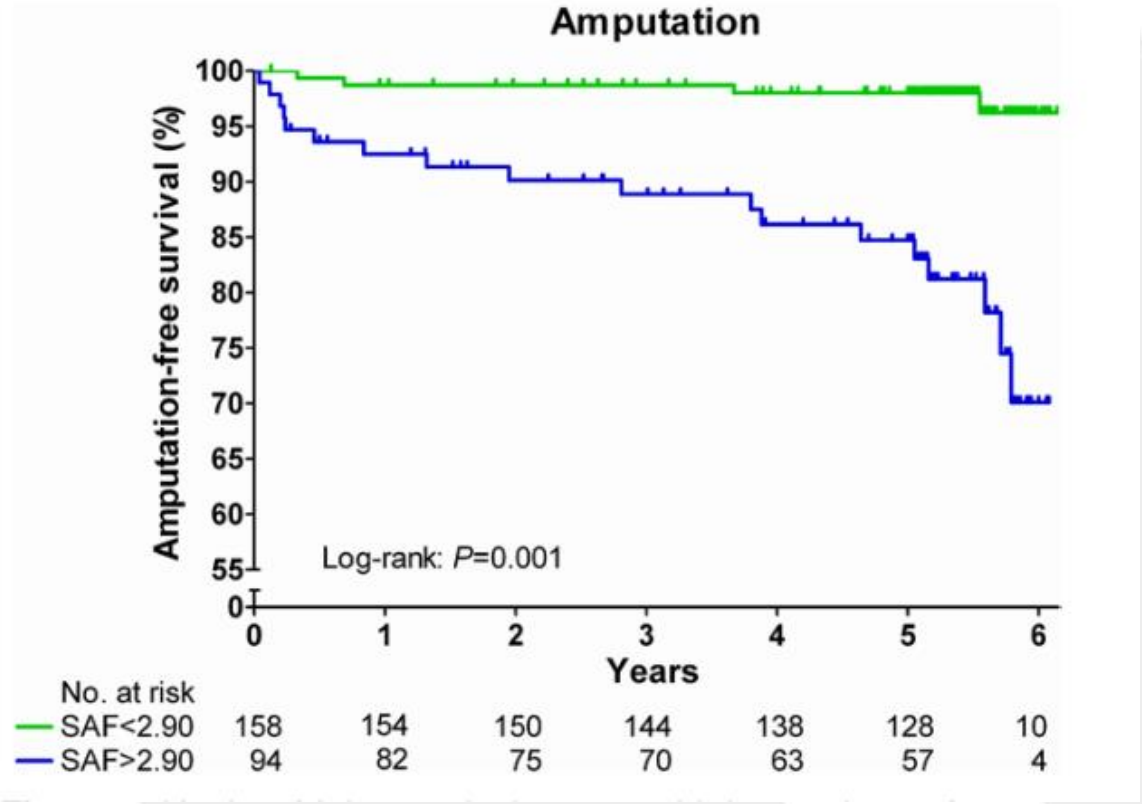
de Vos LC. et al. Arterioscler Thromb Vasc Biol. 2015

4. Atherosclerosis



In this study of 252 patients an AF value >2.9 indicates a risk of amputation within 6 years of almost 10 times higher.

Diagnoptics

Thank you for your attention