Table 1: Validation and Reproducibility studies* in humans for identification / quantification of plaque components and lumen and wall area measurements

	Imaging method	Validation studies (Imaging method versus histopathology)	Reproducibility studies	Comments and Limitations
Identification of plaque components (Present vs. absent)	MRI	N>100; Cohen´s kappa for IPH 0.52-0.95, LR/NC=0.73-0.98 and calcification=0.65-0.75, sensitivity and specificity for IPH 77-100% and 74-100%, LR/NC=82-100% and 65-100%(Ref 23)	N>10; Intra-*reader:* Cohen´s kappa IPH =0.82-0.90, LR/NC = 0.69, calcification = 0.8 (Ref 30) *Inter-reader:* Cohen´s kappa IPH =0.62-0.75, LR/NC = 0.58, calcification = 0.74 (Ref 23 + 30)	Best imaging method for detection of IPH and LR/NC, good reproducibility, extensively validated
	CT	N>10; excellent identification of calcification, debated for all other components	N>3; results and reproducibility vary wildly, small studies only	Best imaging method for detection of calcification; overlap of tissue densities of LR/NC, IPH and fibrous tissue
	US	N>10; Overlap of echolucency between LR/NC, fibrous tissue and IPH (Ref 103)	N>10; no consistent data available, results vary wildly	Can distinguish between echo-lucent and echo-rich plaques but is unable to differentiate between the main plaque components
Quantitative measurements: Lumen and vessel wall	MRI	N>10; Pearson´s R for wall R=0.84 and lumen area = 0.81 (Ref 22)	N>5: *Intra-reader:* ICC lumen = 0.99; ICC wall = 0.98 (Ref 32); CV lumen = 3.2-4.1%, CV wall = 3.4-5.1% (Ref 32) *Inter-reader:* ICC lumen = 0.98-0.99; ICC wall = 0.84-0.90 (Ref 32); CV lumen = 5.3%, CV wall = 7.9% (Ref 32) *Scan-Rescan:* ICC lumen = 0.99; ICC wall = 0.97 (Ref 67); CV lumen = 4.3%, CV wall = 5.8% (Ref 67)	Highly accurate imaging method with excellent reproducibility, wall and lumen area measurements by MRI are ideally suited for cross-sectional and longitudinal studies, measurement errors can be used for power calculation for clinical trials (Ref 67)
	CT	N>10; Pearson´s R for wall area =0.85 (Ref 24)	N>5: *Intra-reader:* CV lumen = 3%, CV wall = 8% *Inter-reader:* CV lumen = 4%, CV wall = 19% (Ref 24)	Calcification can lead to overestimation of wall areas, variability of wall area measurements substantial due to difficulties to delineate the vessel wall from surrounding soft tissue with similar densities
	US	N>5; Pearson´s R for wall = 0.76 (Ref 53)	N >100: 2D-measurements: ICC= 0.65-0.9; CV = 5-20%, data varies wildly (Ref 96); 3D-measurements: *Intra-reader:* CV wall = 2.8-6.0%, *Inter-reader:* CV wall = 4.2-7.6% (Ref 68)	Widely available accurate and reproducible imaging method for CIMT and plaque measurements, Manual measurements are more observer dependent than semi-automatic systems, 3D ultrasound can help to improve accuracy and reliability, Calcification can lead to acoustic shadowing
Quantitative measurements: Plaque components	MRI	N>10; Pearson´s R for LR/NC = 0.75, calcification = 0.74; IPH area = 0.66 (Ref 22)	N>5:*Intra-reader:* ICC LR/NC =0.89-0.99 (Ref 22+32); ICC calcification = 0.9;ICC hemorrhage = 0.74 (Ref 22); CV LR/NC = 8.7% (Ref 67) *Inter-reader:*ICC LR/NC = 0.89-0.93 (Ref 22+32);ICC calcification = 0.9; ICC hemorrhage=0.74 (0.45-0.89)(Ref 22); CV LR/NC=17.6%(Ref 67) *Scan-Rescan:* ICC LR/NC = 0.99; ICC calcification = 0.95; CV LR/NC = 11.1%; CV calcification = 30.8% (Ref 67)	Optimal reproducibility for plaque components, CE-T1 sequences improve delineation of LR/NC, plaque component measurements by MRI are ideally suited for cross-sectional and longitudinal studies, measurement errors can be used for power calculation for clinical trials (Ref 67)
	CT	N>5; Pearson´s R for calcification=0.86 and for LR/NC = 0.48, data for IPH not available	N>5: *Intra-reader:* CV LR/NC = 15%, CV calcification = 8% *Inter-reader:* CV LR/NC = 40%, CV calcification = 8% (Ref 24)	Only tissue component that can be reliably identified is calcification, accurate and reliable quantification of IPH and LR/NC not feasible, automated segmentation might improve the performance

	US	N>5; accurate quantification of plaque components not feasible	N>5; reliable quantification of plaque components not feasible	Not useful for quantification of LR/NC, IPH and calcification
Fibrous cap	MRI	*Identification of FC*: N>5; Cohen´s kappa for intact versus ruptured fibrous cap = 0.74-0.85 (Ref 23) *Quantification of FC*: N>2; Pearson´s R for area measurements = 0.8 (Ref 31)	N>5: *Intra-reader:* Cohen´s kappa = 0.33-0.96 (Ref 29, 30); *Inter-reader:* Cohen´s kappa = 0.26-0.78 (Ref 29, 30) N>1: *Intra-reader:* ICC=0.72 for FC area (Ref 31); *Inter-reader:* ICC=0.78 for FC area (Ref 31)	MRI can identify and quantify the FC with good correlation to histopathology; CE-T1w improves delineation of FC; reproducibility varies wildly, the best sequence to detect FC is still debated
	CT	Identification and quantification of FC not feasible	Not applicable	FC cannot be differentiated from the soft plaque component
	US	N>5; sensitivity and specificity 73% and 67% (Ref 106)	N>10; large variability, operator-dependent	Not the imaging modality of choice to assess the FC
Ulcer	MRA	N > 10; Sensitivity and specificity 80% and 82% (Ref 23)	Good reliability	Good for ulcer detection, CE-MRA superior to non-contrast enhanced MRA
	CTA	N>10; Cohen´s kappa for ulcer detection 0.86 (Ref 25)	Good reliability	Excellent for ulcer detection, superior to CE-MRA due to better spatial resolution
	US	N>10; Sensitivity 33-75%, specificity 33-92% (Ref 106)	N>10; large variability, operator-dependent	US is not the imaging method of choice for ulcer detection; detection can be improved with CE-US and 3D methods
Plaque Inflammation and Neovascularization	DCE-MRI	N>10; Pearson´s R for k-trans vs. macrophage content = 0.75 Pearson´s R for v(p) vs. neovasculature = 0.68 (Ref 40)	N>3; no sufficient data, reported reproducibility varies wildly, dependent on pharmokinetic model and on type of contrast agent	Quantification of inflammation and neovessel density feasible; no consensus on best technique, results are not comparable across centers, only for research studies
	CT	N<3; Pearson´s R for carotid plaque enhancement vs. microvessel density = 0.53 (Ref 49)	N<3; No statistically significant difference between observers (Ref 49)	Requires pre- and post-contrast scan (increased radiation), only for research purposes
	CE-US	N>10; Pearson´s R** for neovascularization 0.88 and 0.78 for inflammation (Ref 46)	N=5; no reliable and consistent data available	The use of microbubbles allows detecting and quantifying neo-vascularization and inflammation. No clear consensus on evaluation. Method operator-dependent
	FDG-PET/CT	N>10; FDG uptake vs. macrophage content Pearson´s R = 0.70 FDG uptake (mean TBR) vs. CD68 as marker of inflammation Pearson´s R = 0.85 (Ref 38)	N>10; *Intra-reader:* ICC = 0.93-0.98 (Ref 37); Inter-*reader:* ICC = 0.71-0.92 (Ref 37) N>1; *Scan-Rescan:* ICC = 0.79-0.92 (Ref 37)	Best imaging method for accurate and reliable detection of plaque inflammation; main disadvantage is the high radiation dose, has the same limitation for other plaque components than CT alone

* Studies were selected by the authors based on impact factor, number of citations, date of occurrence (older papers / landmark papers were preferred) and type of statistical methods (papers with similar statistical methods were preferred to facilitate the comparison of the results); ** originally R^2-values were used in this paper; N=number of studies; MRI = Magnetic Resonance Imaging; IPH = Intra Plaque Hemorrhage; LR/NC = Lipid-rich / Necrotic Core; CT = Computed Tomography; MRA = Magnetic Resonance Angiography; US = Ultrasound; PET = Positron Emission Tomography; CIMT = Carotid Intima Media Thickness; ICC = Intra Class Correlation Coefficient, CE-T1w= contrast-enhanced T1-weighted sequences, CV = Coefficient of Variation (measurement error); FC = Fibrous Cap, DCE = Dynamic Contrast Enhanced; v(p) = fractional plasma volume; k-trans = transfer constant, FDG = 18F-Fluordeoxyglukose, CE = Contrast enhanced