AGLA Taskforce Atherosclerosis Imaging

Rationale and Concept for a Position Paper on Atherosclerosis Imaging in Primary Care

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Suggested Adivisory Board for VARIFO[a] and AGLA[b]

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[a,b] Gian Luca di Tanna, Prof., SUPSI (statistics, health-economy) agreed

[a,b] Andrea Schütz, lic.iur, Prager Dreifuss (previous swissmedic expert) agreed

[a] Laurant Estoppey, Varifo (Data preparation and analysis) agreed

[a] Flavian Kurth, Varifo (communication / ethics) agreed

[1] VARIFO is scientifically well networked and has expertise in cardiovascular imaging tests that have been practically performed to date (together with the Rodiag X-ray institute in Olten): CMR, nuclear cardiology MPS, coronary calcium scoring, coronary contrast enhanced computed tomography, carotid plaque imaging, cTPA). https://varifo.ch

Cover Letter to AGLA

Olten, 28. September 2023

Dear All

Attached I am sending you my draft for a possible position paper on "Atherosclerosis Imaging" of the AGLA. With the possible introduction of guidelines or recommendations concerning atherosclerosis imaging, numerous questions must be answered (in particular also ethical, statistical and legal aspects). I have therefore assembled a group of experts and have already received written declarations of intent from Prof. Di Tanna (statistics, health economics) and Dr. Schütz (legal aspects, former employee of Swissmedics, questions concerning contract law) (attached). These may also be useful for further processes within AGLA.
I am very pleased to present my abstract on November 13 in Zurich and I am looking forward to further developments regarding atherosclerosis imaging within the AGLA.

Kind regards

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Content:

List of Abbreviations

ARCO	Atherosclerosis Risk on cardiovascular Outcomes Cohort study
ARR	Absolute risk reduction
AGLA	Working group on lipids and atherosclerosis of the Swiss Society of Cardiology
ASCVD	atherosclerotic cardiovascular disease
CABG	coronary artery bypass grafting
CAC	coronary artery calcifications, quantified by Agatston Scores (does not require constrast media injection)
CCTA	coronary computed tomography angiography (requires constrast media injection)
CEA	cost effectivness analysis
CT	computed tomography
cTPA	total plaque area of the carotids is a quantification of the total atherosclerosis burden in the carotid artery and a validated measure of risk for heart and stroke, especially in women.
CV	cardiovascular
CVD	cardiovascular disease
DM	diabetes mellitus
ESC	European Society of Cardiology
NNH	Numbers needed to harm.
NNT	Numbers needed to treat. Calculation: 100 divided by absolute risk reduction. NNT dicreases linearly over time, when the relative risk reduction remains constant over time.
PCI	percutaneous coronary intervention
ROI	return on investment (costeffectiveness analysis)
PROCAM	Prospective Cardiovascular Munster Study
PTP	posttest probability
PV	prevalence
RRR	relative risk reduction
SE	sensitivity
SMW	Swiss Medical Weakly, Journal
SP	specificity
SCORE2/-OP	SCORE2: SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. SCORE2 working group and ESC cardiovascular risk collaboration. *European Heart Journal*, ehab309, https://doi.org/10.1093/eurheartj/ehab309 SCORE2-OP: SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. SCORE2-OP working group and ESC cardiovascular risk collaboration. *European Heart Journal*, ehab312, https://doi.org/10.1093/eurheartj/ehab312
VSL	Value of a statistical life
VLSY	Value of a statistical life per year (according to WHO and referenced by [1], VLSY is calculated by multiplying the individuals gross domestic product (BIP) by 3. Example for Switzerland: 88 209 CHF in 2022 x 3 = 264 627 CHF.

Rationale for a position paper of AGLA regarding Atherosclerosis Imaging: an introductionary note

The presence of major and independent cardiovascular risk factors increase the risk of cardiovascular disease (ASCVD) and these risk factors have been aggregated into cardiovascular risk charts in order to obtain a more comprehensive risk assessment. In Switzerland, the European SCORE2/-OP risk calculators have been adopted and categorize patients as having either low to intermediate, high, or very high cardiovascular risk[2]–[4]. However, Mortensen found statin eligibility using SCORE2/-OP risk assessment and guidelines to dramatically reduce eligibility for primary prevention statins [5]. According to our observation from the ARCO Cohort, 82% of evens occurred in the 3rd tertile of the total carotid plaque area (cTPA) [6], and cTPA maintained prognostic information over and above SCORE2/-OP in middle aged subjects (in press: Swiss Medical Weekly). From this and many other observations, additional emerging cardiovascular risk factors may be needed in order to improve ASCVD risk prediction. However, the integration of Atherosclerosis Imaging into clinical decision making is hampered by a lack of guidelines on how this integration should be performed. Since a higher amount of atherosclerotic plaque burden is associated with higher ASCVD risk [6], methods should be discussed on how to integrate atherosclerotic plaque burden into ASCVD risk [7].

Key Messages

1. Imaging of atherosclerosis, especially cTPA and coronary calcifications, is reliable in risk prediction, reproducible, and cTPA has numerous advantages over coronary calcifications (no cost or radiation exposure, monitoring of atherosclerosis over time possible).
2. The mathematical integration of atherosclerotic plaque quantities into risk prediction is validated (Bayes theorem).
3. The test possibility must be made known to the patients (legal aspect)
4. Atherosclerosis imaging is often decisive in discussions regarding the indication for statins and lifestyle changes.
5. In patients with high-risk atherosclerotic plaque, preventive cardiovascular therapy is mandatory
6. There is no need for randomized controlled studies to initiate a preventive medical therapy in patients with athrosclerotic plaques evidenced by imaging.
7. cTPA is the best suited test to monitor atherosclerosis over time

Methods and Rationale for Atherosclerosis Imaging and Atherosclerosis Monitoring with Imaging

Atherosclerosis is a frequent cause of ASCVD world-wide [8] and can be diagnosed and quantified with Atherosclerosis Imaging [9], [10]. Higher amounts of atherosclerosis are related to higher ASCVD event rates [6], [11]–[15].

Atherosclerosis Imaging methods are increasingly available and different anatomical and functional imaging techniques are available such as computed tomography, magnetic resonance, ultrasound, positron emission tomography, near-infrared fluorescence, nano-particle imaging, molecular imaging, optical coherence tomography and functional imaging [16]. Despite the plethora of Atherosclerosis Imaging methods, a complete assessment of plaque vulnerability could not be achieved [17]. This is in line with the concept of global atherosclerotic disease burden for cardiovascular risk assessment that goes away from individual vulnerable plaque lesions [18]. For the clinician in daily primary-care practice, fancy and experimental radiology is usually non available for personalized cardiovascular risk assessment and the reliance on readily available imaging methods are favored, e.g. ultrasound of carotid and femoral arteries or a plain coronary CT scan without contrast media for the assessment of coronary calcifications and their quantification (Agatston Score, calcified coronary plaque volume). Atherosclerosis Imaging of carotid plaque using the total plaque area (cTPA) is cost-effective [19] and coronary calcium (CAC) as well as carotid plaque quantification using cTPA can be imaged with high reliability and reproducibility [20], [21]. Furthermore, Atherosclerosis Imaging is well suited to observe changes in atherosclerotic burden over time [22]–[31] and patients with carotid plaque regression or stabilisation encur about 50% less ASCVD events [32], while CAC is not suited to observe plaque regression over time, because statins increase – due to the healing process of inflammed atherosclerotic leasons - the amount of CAC [33], [34]. Imaging may also be used to observe effects of medical intervention over time as a surrogate marker for cardiovascular events [35]. Others have found a linkage between changes in plaque amount over time and ASCVD events [22], [32], [36]–[38]. As stated by [37]: “Plaque progression precedes cardiovascular events [37]; If outcome data linking plaque regression to reduce CV events emerge, monitoring the response to coronary plaque treatment may ultimately supersede surrogatemarkers like risk scores and lipoprotein levels”. Therefore, the new paradigm of treating arteries instead of risk factors [39] receives more scientific evidence and serial imaging of the global plaque burden, e.g. in the carotid arteries appears most suitable for atheroscerosis management using cTPA [40]–[42].

Is Atherosclerosis Imaging performed in Switzerland?

To the best of our knowledge there are no survey data about the use of Atherosclerosis Imaging in Switzerland. However, doctors use Atherosclerosis Imaging with ultrasound insonating predominantly carotid and abdominal arteries as known from personal communications. Furthermore, coronary imaging using contrast enhanced computed tomography angiograhy (CCTA) is also commonly available in radiology institutes. Usually, physicians have no tools at hand that enable them to integrate findings from Atherosclerosis Imaging into a more personalized global risk quantification and categorization. That is why we have developed and validated posttest risk calculators that integrate the prior probability for ASCVD, e.g. with SCORE2/-OP (also termed prevalence in the Bayes theorem), into the possttest or posterior probability, available at https://varifo.ch/score2-rechner/.

Should Atherosclerosis Imaging guide clinical decision making?

Since most cardiovascular events occur in patients at low cardiovascular risk [6], risk modification using emerging cardiovascular risk factors such as Atherosclerosis Imaging are recommended by the ESC and by AGLA [43]: “Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individualsat low or moderate risk”. The ESC key message regarding risk modifying cardiovascular risk factors was: “Certain individuals declare themselves to be at high or very high CVD risk without needing risk scoring, and all risk factors require immediate attention. This is true for patients with documented CVD, older individuals with long-standing DM, familial hypercholesterolaemia, chronic kidney disease, carotidor femoral plaques, coronary artery calcium score >100, or extreme Lp(a)elevation”. ESC defined the following findings as categorizing patients to very high risk as follows: “Documented ASCVD, either clinical or unequivocalon imaging. Documented ASCVD includes previousACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterialrevascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiographyor CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.” Regarding predictive values of imaging, the ESC stated: “Assessment of carotid or femoral plaque burden with ultrasound has also been demonstrated to be predictive of CV events, comparable to CAC [11], [44], while the measurement of the carotid intimamedia thickness is inferior to CAC score and carotid plaque detection [45]–[47]. Arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk: **Class IIa** recommendation, level of evidence B. CAC score assessment with CT should beconsidered as a risk modifier in the CV riskassessment of

asymptomatic individuals at low or moderate risk: **Class IIa** recommendation, level of evidence B".

Radiation Burden

One advantage of measuring cTPA instead of coronary calcifications lies in the fact, that computed tomography has an inherent radiation associated cancer risk [48]. Especially serial testing with accumulated lifetime doses is associated with 42 cancer cases per 100 000 men exposed to a cumulative dose of 2.4 mSv and is 62 cancer cases per 100 000 in women.

Guidelines for Plaque Quantification and Clinical Integration

Atherosclerosis is a major cause of mortality, morbidity, disability, and direct and indirect societal costs in Switzerland. Currently, SCORE2 and SCORE2/-OP should be used as a baseline test (which determines a prior probability of ASCVD in 10 years). Because of problems with the sensitivity and specificity of SCORE2 and SCORE2/-OP, additional information from atherosclerosis imaging is needed to further stratify and personalize ASCVD risk. Technically, carotid plaque imaging results (total plaque area) and coronary calcification (Agatston score) are used to calculate posttest risk using the Bayes theorem.

The proposal for sequential testing with carotid atherosclerosis imaging is based on the observation that most ASCVD events occur in healthy individuals who are classified as low to intermediate risk [49], [50]. Therefore, additional information may be needed to identify individuals at higher than expected risk. Atherosclerosis imaging is proposed as a solution, first determining total carotid plaque (cTPA) and then, in individual cases, coronary artery calcium levels as sequential tests in addition to SCORE2/-OP results [10].

In Switzerland, there are no published guidelines for the quantification of atherosclerosis and the way, how such plaques should be intergrated into cardiovascular risk management. In constrast to established cardiovascular risk factors, AGLA has established clinical pathways to treat cardiovascular risk based on SCORE2/-OP. At least for quantified carotid and coronary plaques, clinical pathways should be available to clinicians in order to guide the intensity for preventive therapies.

Using plain CT, coronary calcifications can be quantified with calcified plaque volume and Agatston scores based upon a slice thickness of 2.5 mm and a predefined field of view [51]. Vendors of CT Systems usually furnish a software to calculate global calcified coronary plaque burden by giving the result as Agatston scores, percentiles of calcification, and calcified coronary plaque volumes. Contrast enhanced coronary angiography with CT (CCTA) allows to image additionally non-calcified coronary plaques that can be automatically detected and quantified regarding fibrous and lipid-rich plaques on coronary vessel base.

Carotid plaque can be best and reliably quantified using carotid total plaque area (cTPA) [3], Table 4.

Based upon cardiovascular outcome studies, amounts of Agatson Scores and cTPA have known sensitivities and specificities, from which posttest risk calculations using the Bayes Theorem [7] can be used to modify SCORE2/-OP cardiovascular risk and associated predictive ratios can be validated using outcome data [52].

cTPA should be measured as follows (https://varifo.ch/tpascore2/):

Head position angled 45°, subject may be sitting, standing, or lying down.

Visualization of arteries from different angles (anterior to posterior) and transversely as well as longitudinally along the entire length of the carotid artery (clavicle to mandibular angle) and femoral arteries (all, as far as visible) [10].

Definition of plaques: > 1 mm thickness = plaque

Plaque tertiles: 1-21 (low risk), 22-62 (intermediate risk), > 62 mm^2 (high risk)

Very high ASCVD risk of 20% or more in 3 years: TPA >140 mm^2 [6].

Pitfalls: lipid-containing plaques may be missed, possibly work with color Doppler.

Due to calcifications in large plaques, large plaques cannot always be measured exactly, but this has no relevant influence on risk stratification, as these are usually high-risk plaques.

However, for follow-up purposes, it is useful to determine TPA as accurately as possible.

In individuals with intermediate or high risk according to SCORE2 and carotid atheromas < 22 mm^2, the total plaque area (TPA) should also be determined from longitudinal atheroma sections of the femoral artery. This additional information is rarely required and eliminates an underestimation of the risk due to small carotid atheromas.

Mathematically, Bayes theorem calculates posttest risk using the pretest probability (SCORE2 = prevalence) if the imaging test is positive (PTP pos: e.g., Agatston score >0, total carotid plaque area >21 mm2), otherwise the formula PTP neg is used [7]:

PTP pos: (PV x SE)/[PV x SE + (1 - PV) x (1 - SP)]

PTP neg: [PV x (1 - SE)]/[PV x (1 - SE) + SP x (1 - PV)]

From the four-field table, the sensitivity and specificity of a test can be derived:

https://www.kardiolab.ch/BayesCalcTab.html

The result to SE= sensitivity, SP = specificity: the following numbers are used:

cTPA Tertiles	SENS	SPEC
cTPA 0	98.7	27.01
cTPA <22 mm2	98.70	27.01
cTPA 22-61 mm2	95.45	52.42
cTPA >61 mm2	81.82	78.39
CAC tertiles	SENS	SPEC
CAC 0	93.0	34.0

CAC 1-100	93.0	34.0
CAC 101-300	72.0	75.0
CAC >301	54.0	86.0

cTPA SENS SPEC is derived from the ARCO study [6], CAC SENS SPEC is derived from the Gudmundsson study [51]. SCORE2/SCORE2-OP with Bayes theorem results for TPA and CAC is available as an Excel calculator (https://varifo.ch/wp-content/uploads/2023/02/TPASCORE2A.xlsx). Traditionally, patients are categorized as low, intermediate, high, or very high risk for a particular disease, such as myocardial infarction or stroke, or a combination of both (ASCVD). In SCORE2/-OP, the risk categories are low to moderate, high, very high, and patients are categorized based on age and absolute risk (e.g., a person aged <50 years is at high risk if the absolute risk is equal to or greater than 2.5%). According to the 2021 ESC treatment recommendations, lipid interventions are defined based on the SCORE2/-OP.

Sex aspects of Atherosclerosis Imaging

An important aspect of Atherosclerosis Imaging has to be considered regarding occurrence and quantity of atherosclerosis in different vascular beds, particularly regarding sex-associated effects on atherosclerosis imaging in women. There is increasing evidence that carotid plaques may have advantages in women: 1) Early evidence for better risk prediction in women than coronary calcium scores [51]; 2) Better risk prediction for myocardial infarction in the Tromso study in women than in men compared with traditional risk tables [53], [54]. In the Nixdorf Recall Study with up to 20 years of follow-up, 28% of events occurred in women with an ASCVD 10-year risk <7.5% and a CAC <100, whereas only 9% of events occurred in men in this risk category [55]. In the Gudmundsson 2022 study, carotid plaques were directly compared with coronary artery calcifications in men and women separately (refer to Table 2 in the paper). In women without CAC, 41% had minimal or significant atherosclerosis in the carotid arteries (in men, 21%). Among women with CAC, only 5.6% had no carotid plaques (in men: 4.6%). CAC>300 without carotid plaque was found in 0.6% of women (in 1.1% of men) [51]. This is also true in our Swiss population, in which we compared men and women with CAC and TPA, as shown in our submitted abstracts: TPA is highly prevalent in female (men: 73%) cardiology patients (67%) and of these, 36% were significantly more likely to have no CAC than men (22%) [date on file Varifo Foundation].

Legal and societal aspects of Atherosclerosis Imaging

The epidemic of atherosclerosis, although treatable to a large extent, is still far too often causing morbidity and and cardiovascular death in Switzerland. Prevention of the consequences of atherosclerosis may well be subject to change in society: do we need good prevention at all, when more and more old people are causing high societal costs?

The narrative of (too) high costs in health care has been successfully established by the health insurance lobby and its associated health economics [56]. This is because the latter focuses on the costs of prevention without estimating the medical and social costs of preventively avoided diseases. Ageism is only one observable consequence of this.

Unfortunately, other factors such as the cholesterol and statin lies are also trying to destroy preventive efforts at the micro level of the doctor-patient relationship. Another development concerns the individualization of the medical "offer" through education and exploration of patient preferences. Paradoxically, in times of rationing of medical services, movements such as "smarter medicine" open up a broad paternalistic field of physician recommendations with withholding effective options by generating feelings of futility ("futility in medicine") coupled with a partly irrational fear of violating the "natural" human body in the evolving concepts of "medical humanities."

As a consequence, societal environment is increasingly unfriendly to healthcare. This, of course, has implications for the safety of care and patient safety. The mission of the AGLA is to develop recommendations for the prevention of preventable cardiovascular events and thus establish a medical service that serves the preferences of patients. Therefore, at the time of consultation, the physician must always be sure that he or she has correctly identified the patient order.

Example of a patient order: "I want to stay healthy until 90. What should I do?"

In Switzerland, the doctor is subject to the code of obligations (https://www.fedlex.admin.ch/de/cc/internal-law/22), which means that a doctor needs the patient's explicit consent to perform or refrain from performing a medical treatment. The doctor is obliged to refuse treatment if he is unable to fulfill the patient's order for any reason. For example, if the physician does not have the necessary knowledge, skills, or resources to provide the required treatment, or is unable to provide the treatment due to ethical concerns or legal requirements, he must refuse the patient. In this case, the physician must communicate to the patient his or her reasons for refusing treatment and, if appropriate, offer an alternative solution.

A physician who conceals preventively effective medical measures, e.g. statins, from the patient and instead imposes his own conviction about the impact of statins on morbidity (the so-called cholesterol lie) violates the code of obligation in Switzerland. The physician has – defined by Swiss law

– the duty to provide treatment carefully and conscientiously, which means that he must provide the patient with all the relevant information so that the patient can make an informed decision about indicated treatments. If the doctor withholds information that could be relevant to the patient's decision, he violates his duties as a contractor. It is also important to note that the code of obligation in Switzerland is based on the voluntary expression of the patient. The physician is obligated to obtain the patient's consent before providing or withholding treatment. If the physician withholds information from the patient and thus prevents the patient from making an informed decision, the patient's consent is given on an uncertain basis, which constitutes a violation of the code of obligations. Part of the information regards the possibility of imaging atherosclerosis and physicians should inform patients about these diagnostic options, e.g. when patients are sceptical about statins but would consent to be treated with statins if atherosclerotic plaques are present. The medical law in Switzerland is concretized in the Code of Obligations (e.g. Art. 396 OR).

Should atherosclerotic plaque prompt and guide preventive medicine? Ethical aspects.

Numerous studies have documented that treating cardiovascular risk factors lowers both cardiovascular risk and reduces non-calcified atherosclerotic plaque burden even in advanced stages of atherosclerosis [57]–[59]. From animal studies it is known that aggressive LDL cholesterol lowering to 0.3-0.9 mmol/l reduced plaque leason area significantly also in advanced atherosclerotic plaques [60]. The reversibility of atherosclerosis with preventive intervention is a clinically relevant aspect, as extensively shown for lipid lowering drugs [22], [24], [27], [29] and the improved prognosis with regression of coronary [25] and carotid [32], [61] atherosclerosis. Tracking carotid atherosclerosis over time using a test that incorporates carotid total plaque area (cTPA) has been shown to reduce cTPA in more than 10’000 intensively statin treated patients by Spence in Canada [61], by Herder in Norway [62] and by Sturlaugsdottir in Iceland [42]. Since statins reduce cardiovascular risk and since cTPA regresses or progresses slower with statins or more intensive statin use, current evidence gives support for the idea that carotid plaque regression or stabilization is most likely to improve cardiovascular outcome. This is further supported by Spence et al, where no progression or a reduction of carotid plaques over time was a statistically significant predictor for fever cardiovascular events during follow up [32].

As to the best of our knowledge, there is no formal proof for the concept available from controlled randomized and placebo-controlled interventional studies that in humans treated cardiovascular risk factors simultaneously reduce cardiovascular events and atherosclerotic plaque burden. Only evidence from observational studies show fewer cardiovascular events in patients with stabilized or regressed plaque amounts [32], [61].

Is it ethical to wait for such randomized clinical trials?

The question of whether it is ethical to wait for randomized clinical trials to treat cardiovascular risk factors is a complex one. Randomized clinical trials are considered the gold standard for evaluating the efficacy of treatments. Current evidence creates a situation where waiting for such trials may not be ethical. For example, there is already strong evidence that treating cardiovascular risk factors reduces cardiovascular risk and reduces non-calcified atherosclerotic plaque. There is overwhelming evidence in favor of this association and no evidence for the contrary effects, e.g. an excess of non-calcified atherosclerotic plaque growth in those treated for cardiovascular risk factors when compared to patients not treated for these cardiovascular risk factors (PubMed search 25.07.2023). Evidence shows that non-calcified atherosclerotic plaque growth is associated with an increased risk of cardiovascular events. This association has been found in a variety of populations, including those with and without traditional risk factors for cardiovascular disease. In contrast, there is no evidence that treatment for cardiovascular risk factors, such as statins, leads to non-calcified atherosclerotic plaque growth.

Important amounts of atherosclerotic plaque evidenced by cardiovascular imaging automatically transfer primary care patients into the very high risk category, as defined by the European Society of Cardiology [43]. From what is recommended in these guidelines, patients with relevant amounts of atherosclerosis evidenced by imaging must be treated with known cardiovascular preventive therapies in order to achieve the predefined treatment goals of very high-risk patients. In our observational study, there were significant protective effects observed in those with advanced carotid atherosclerosis and statin treatment [63].

Withholding cardiovascular preventive therapies is neither recommended nor ethical in those with documented relevant amounts of atherosclerotic plaques detected by imaging, which is also true regarding elderly men and women [64]. It is unethical to perform a controlled randomized and placebo-controlled interventional study in humans with atherosclerotic plaque. Such a study may only be confined when early stages of atherosclerosis are present and where cardiovascular risk of cardiovascular events in the placebo treated arm are very likely to remain low. Such a trial was proposed by Jennifer Robinson in 2018 in the “Proposed CURE ATHERO Trial” [65].

The overwhelming evidence shows that plaque regression is an important clinical and therapeutic goal. In subjects with plaque progression, intensified preventive therapy is mandatory. cTPA appears to be a test especially attractive for serial testing over time in order to observe the effects of prevention on subclinical atherosclerosis (Table 4) and helps patients to improve their cardiovascular risk.

Cost-effectiveness of Atherosclerosis Imaging

What is the associated cost-effectiveness of Atherosclerosis imaging in terms of medical and social or indirect costs due to preventable cardiovascular events? Factors that influence cost-effectiveness are the duration of treatment, e.g., with statins, the price of the intervention and effects regarding absolute risk reduction of morbidity and mortality. Atherosclerosis imaging modifies absolute risk and thus has a direct impact on cost-effectiveness and NNT. Unfortunately, too often NNT is not communicated in relation to the treatment time. Cholesterol opponents use an NNT per one year of treatment, leading to very high NNT of > 100, as debated in the Schweizerische Aerztezeitung [66]. The criterion for treatment decisions based on NNT after one year is non-existent in the literature because atherosclerosis is a chronic disease that progresses over decades and the effectiveness of statins increases with treatment duration over these decades. The NNT must always be linked to the duration of treatment. One of our studies shows that carotid ultrasound significantly improves cardiovascular risk stratification and is cost-effective [67]. The Swiss Medical Board QALY model has several drawbacks, highlighted in our sensitivity analysis, in which results vary substantially and are not useful for clinical decision making [68]–[70]. A "treat them all" strategy with statins in the Swiss population aged 30-65 years may be cost-effective when the indirect costs of preventable cardiovascular events are included, even with an unacceptably low value of a statistical life year. Models of cost-effectiveness should not necesseraly include quality-adjusted-life-years (QALY) of patients *and* relatives, but should use the value of a statistical life year (VSLY), in order to include costs to societies for lost life years, and should include indirect costs of survived cardiovascular events.

Disease Compression and cardiovascular prevention

Therapeutic advances in modern medicine prevent mortality caused by previously lethal diseases, with the result of increasing the number of non-communicable chronic diseases in the elderly [71]. Therefore, a greater proportion of the gross domestic product is required to cover increasing costs of partially more expensive cures made available to a greater proportion of the population [72]. Higher costs lead to the proposition of rationing therapeutic interventions, as these would appear financially unsustainable, for example due to “toxic pricing” in the pharmaceutical industry [73]. As a result, the industrialized nations are now in the remarkable position of being --to a certain degree--victims of their medical success.

Despite the positive effects of medical progress, Ernest M. Gruenberg offered a more negative perspective in a report issued by Milbank quarterly in 1970[1]. Gruenberg argued that the ability of modern medicine to prevent death could have negative effects, due to an expansion of disease,

which he termed “failures of success”: An increasing number of survivors could be affected by an increasing number of diseases (expansion of morbidity). Further negative aspects of modern medicine have been posited in the form of iatrogenic and pathogenic effects [74] as well as the expansion of medical indications in curative and palliative therapies, and the financial consequences thereof [75].

Medicine has the potential to be highly effective in prevention of morbidity and mortality, but there remain challenges in the realization of this potential. A common negative attitude towards “medical interference” leads to a purposeful exaggeration of side effects and a downplaying of beneficial effects [76]. Consequences are not only a resistance towards vaccinations [77], but also possibly substituting palliative medicine with assisted suicide using Pentobarbital (as supported by the organization EXIT in Switzerland). Such movements are reconcilable with the utilitarian viewpoint of minimizing “waste” of limited resources [78]. At the same time, an economic view of society comes to bear when an economic value of the productivity of a human being is implemented in a decision to withhold expensive therapies on the base of quality adjusted life years (QALY) [79]. “Why I hope to die at 75”, published by the bioethicist Ezechiel Emanuel underlines the prioritization of economic values with respect to the use of medical services, which are perceived to be too costly [80].

The positive view of the situation is completely different, as diseases may be prevented until natural death occurs. This hypothesis was considered in 1980 by James Fries [81], and has been verified on the base of a cohort study over 40 years: Individuals with a favorable risk profile for cardiovascular diseases had an absolute compression of all-cause morbidity and associated costs at the end of observation after 40 years [82].

There is a simple mathematical relationship between risk of morbidity and a high expectancy for healthy life years (for example at the 90% level). We calculate a ‘risk compression paradox’ as follows:

Years in full health with a probability of 90 % = (100 % / % risk in 10 years)

As can be seen in the figure below, a high probability (90%) to experience healthy years increases exponentially, when the risk of morbidity lies below 15% in 10 years. The expansion of healthy years due to compression of morbidity is unexpectedly high, when we lower the risk even further (for example from 7% to 2%, with a hypothetical gain of 36 healthy life years). However, individuals with a higher risk of morbidity will not benefit from a similar gain, when their risk is reduced equally (by 5%) because of disease substitution effects, e.g., in smokers treated with statins, while cessation of smoking produces compression of morbidity because of the many diseases associated with smoking [83]–[88]. This highlights the importance of treating all treatable risk factors as well as possible in order to achieve disease compression.

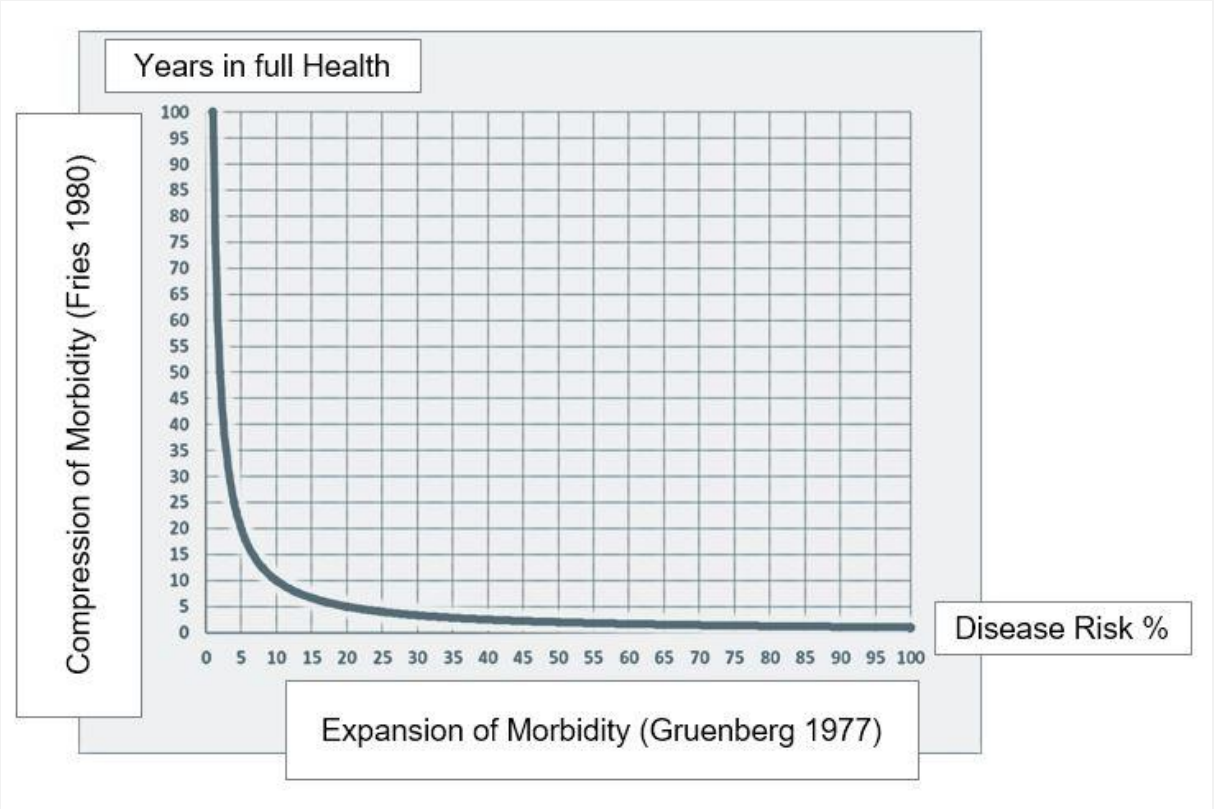
Education, encouragement of compliance and financial support can increase the effectiveness of

preventive medicine, resulting in a shift from disease expansion to disease compression. Improving prevention is an inevitable requirement in the solution of the problem of disease expansion. The optimization of evidence-based prevention must be the focus of public health, also in the creation of a climate of trust in the benefits of preventive medicine, while weakening scientifically unsustainable arguments against prevention by educating the public.

In counselling the healthy and patients in primary care, further research is required to develop adequate risk models that accurately measure risk for all-cause morbidity. Whether all-cause morbidity can be calculated by using the Framingham risk equation for cardiovascular disease or SCORE2/-OP and a simple multiplication factor or if additional modifiable risk markers should be incorporated in such risk models should be a matter of investigation.

Figure: The graph displays the "risk compression paradox", with the hypothetically expected number of healthy years on the vertical axis and disease risk in percent on the horizontal axis. Suggested reading: Risk of morbidity is calculated for 10 years, and the curve displays the expected years in health with a certainty of 90% for each risk level. Example: a) the risk of morbidity in 10 years is 50%, thus a risk of 10% is reached in 2 years; b) the risk of morbidity in 10 years is 2%, so that a risk of 10% is reached after 50 years.

Following assumptions are made: Risk increases linearly, and remains at the same risk level over time. The formula to calculate expected years in full health with a probability of 90 % = (100 % / % risk in 10 years)



SWOT Analysis

Strengths:

Risk modification: Ultrasound based atherosclerosis Imaging to obtain carotid total plaque area (cTPA) is a strong and clinically important risk modifier regarding cardiovascular risk assessed by SCORE2/-OP (in press SMW, [89]) or PROCAM/SCORE [6] . Based upon published sensitivites and specificities and the Bayes theorem[7], posterior likelihood ratios become available and modify initial risk assessments with high accuracy [52].

Feasability, reliability, cost-effectiveness: Carotid TPA is cost-effective in primary care [67] and has very good reliability [20]. The cTPA test can be easily learned and used by general practionars (how-to-do informations are also available at https://varifo.ch/tpascore2/).

Comparison with calcium scoring: Recently, direct comparison of cTPA with coronary calcifications has become available in our practice based Swiss Cohort [90] and was also discussed by Spence [91], [92]. Carotid plaque are closely correlated with coronary calcium [51]. This is also supported by a metaanalysis (submitted) [93].

Atherosclerosis management: Most importantly, cTPA can be repeated at low cost and with high reliability [20] in order to monitor treatment effects over time in primary and secondary care. The concecpt of arterial age derived from cTPA is clinically validated as an important step in patient management, according to the paradigm treat arteries, not risk factors [39].

Opportunities:

Medical Networks such as Sanacare / Centramed have already expressed their vivid interest in risk modification using cTPA. Strong opinionleaders are required to further promote cTPA in preventive medicine. Ultrasound cTPA should be framed regarding accuracy, ethics, legal, and cost utility aspects (https://varifo.ch/nationale-arbeitsgruppe-atherosklerose/) on behalf of a working group that eventually creates a position paper. More clinically acting partners may receive alterts about cTPA, eventually a cTPA Network can be created.

Further research:

1. 20 year follow-up of cTPA in cardiology practice based patients in primary and secondary prevention settings in relation to major independent cardiovascular risk factors and outcome.
2. Correlation of cTPA with coronary calcifications and non-calcified coronary atherosclerotic burden (see Appendix for an example): using validated coronary CT software (GE Healthcare) and a brand new coronary CT equipment, quantification of mixed, soft, and calcified plaque of the whole coronary tree is possible.
3. Develop calculators that derive biological age from risk factors and arterial age.
4. Long-term comparative outcome studies of cTPA and coronary calcifications, stratified by sex:

there is emerging evidence, that cTPA is a stronger risk factor in women than in men [54]

Weaknesses:

Although the rate of missed cardiovascular events in patients with cTPA is low (about 15%, [6]), additional Atherosclerosis Imaging studies should be carried out in patients with unexpectedly low carotid atherosclerosis. Usually, femoral atherosclerosis assessment is the next step and if doubts about the validity of the results remain, a coronary computed tomography non-contrast enhanced calcium score may be obtained [90].

Threats:

The validity of cTPA may be questioned by opinion leaders in order to serve their own agenda, especially regarding the lack of randomized trials, where Atherosclerosis Imaging based risk modification has not yet been studied.

Conclusions

Thus, in summary, carotid TPA is a reliable and reproducible tool for the detection and treatment of atherosclerosis in men and probably even more so in women. It is a cost-effective, low-cost, radiation-free, software-free, quick-to-learn, bedside imaging modality that is widely available using linear ultrasound probes, can be integrated into cardiovascular risk calculators using the BAYES theorem and does not incur additional costs. The test has been validated and should be included in the detection and treatment of ASCVD risk in Switzerland. In contrast to coronary artery calcification (CAC) measurement, whose cost-effectiveness is unknown, at least in Switzerland, is radiation and software dependent, and is not performed at the bedside, cTPA undoubtedly offers significant advantages over CAC, especially in women.

Table 1: Criteria for additional screening test quality (adopted from [7])

1. Independent comparison with a gold standard
2. Large spectrum of pretest probabilities
3. Ability to change clinical decisions
4. High reproducibility
5. Validation in several populations
6. High accuracy to discriminate individuals with and without disease discrimination

Table 2: Direct comparison of coronary calcium scores and carotid total plaque / carotid plaque volume:

BioImage [11]	**N**	**AGE (y)**	**FRAM 10y**	**FU**	**CVD***	**Modality**	**CVD****	
	5808	68.9	9.20%	2.7	216 (4.2%)	TRF	1.00	
						CCS	2.87 (1.73–4.74)	
						CPV	2.97 (1.92–4.60)	
MESA [94]	**N**	**AGE (y)**	**Risk 9.5 y**	**FU**	**CVD*****	**Modality**	**CVD**	**Stroke/TIA**
	6779	62.2	7.90%	9.5	7.90%	TDF	1.00	1.00
						CCS	3.12 (2.44-3.99)	1.54 (1.09-2.18)
						CP****	1.61 (1.17-2.21)	1.40 (1.35-1.45)
						CIMT 75%	1.20 (0.94-1.52)	1.01 (0.70-1.47)
						Modality	**AUC CVD**	**AUC Stroke/TIA**
						TDF	0.756	0.782
						CCS	0.776 (p 0.001)	0.785 (p NS)
						CP****	0.760 (p 0.03)	0.787 (p 0.045)
						CIMT 75%	0.757 (p NS)	0.783 (p NS)

Legend:

* CVD: Death, AMI, STROKE, UAP, REVASC

** 3rd versus 1st tertile adjusted for: diabetes mellitus; current smoking; body mass index; systolic blood pressure; antihypertensive agent use; low-density lipoprotein cholesterol;

*** CVD fatal or non-fatal myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (followed by coronary revascularization), stroke (fatal or non-fatal), other atherosclerotic CVD death

**** included 3310 participants with re-read carotid ultrasound only.

TDF traditional risk factors

CCS coronary calcium score

CPV carotid plaque volume

CP carotid plaque

CIMT75% CIMT above 75% percentile

Table 3: Frequently used parameters for the quantification of carotid plaques

Plaque characteristic	**measurements**	**First author and reference**
Thickening of IMT	> 1.0 mm	Spence 1997 [95]
doubling of IMT thickness		Spence 1997 [95]
doubling of IMT thickness		Mannheim Consensus [96]
Thickening of IMT	> 1.2 mm	Handa [97]
Subjective assessment		Polak [98]
Encroaching into the lumen	0.5 mm	Mannheim Consensus [96]
Thickening of IMT	≥ 1.5 mm	Mannheim Consensus [96], Spence [32]
texture changes		Singh [99]
Plaque yes or no		Nambi [100]
Subjective assessment	plaque burden none to severe	Peters [101]
Plaque presence	number of plaques	Plichart [102]
Plaque thickness	in mm	Rundek [103]
plaque area	in mm^2	Spence [32]
plaque volume	in mm^3	Baber [11]
Echo lucency	gray scale	Stein [54]
Contrast Agent	plaque vascularity	Coli [104]

Table 4: Classification of various imaging parameters of the carotid arteries regarding in clinical practice (authors personal view)

	Availa-bility	Repro-ducibility/ Feasibility	Radi-ation	Little training needed	Low Cost	Brief exami-nation	Tracking over time	Vendor indepen-dent	Validated for outcome	**Sum Score**
carotid total plaque area	3	3	3	3	3	3	3	3	3	**27**
femoral plaque	3	3	3	3	3	2[a]	2[b]	3	3	**25**
ankle-brachial index	3	3	3	3	3	2	3	2	3	**25**
aortic plaque	3	2	3	3	3	3	1[c]	3	3	**24**
carotid plaque height	3	2	3	3	3	3	2	3	2	**24**
carotid plaque density	3	2	3	2	3	2	1	3	2	**21**
carotid plaque ulcerations	3	2	3	2	3	2	1	3	2	**21**
carotid total plaque volume (Philips)	1	3	3	1	1	1	3	1	3	**17**
CMR Plaque Imaging	1	3	3	1	1	1	3	1	2	**16**
carotid IMT	2	2	3	1	2	1	1	1	2	**15**
contrast enhancement (CEUS)	1	3	3	1	1	1	3	1	1	**15**
coronary calcium score	1	2	0	1	1	1	0	1	3	**10**

[a] access limited with clothes. [b] not established. [c] difficult to quantify true size with ultrasound (suprasternal view).

Source of tables 2-4: [10]

Literature

[1] R. Schleiniger, “Der Wert des Lebens: Methoden, Empirie, Anwendungen,” *ZHAW*, no. August, 2006, [Online]. Available: https://digitalcollection.zhaw.ch/bitstream/11475/16911/3/DerWertdesLebens.Bericht_2006_SC3.4.pdf

[2] S. working group and E. C. risk Collaboration *et al.*, “SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe,” *Eur Heart J*, vol. 42, no. 25, pp. 2439–2454, 2021, doi: 10.1093/eurheartj/ehab309.

[3] S.-O. working group and E. C. risk collaboration *et al.*, “SCORE2 Old,” *Eur Heart J*, Jun. 2021, doi: 10.1093/eurheartj/ehab312.

[4] S.-D. W. G. and the E. C. R. Collaboration *et al.*, “SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe,” *Eur Heart J*, May 2023, doi: 10.1093/EURHEARTJ/EHAD260.

[5] M. B. Mortensen, A. Tybjærg-Hansen, and B. G. Nordestgaard, “Statin Eligibility for Primary Prevention of Cardiovascular Disease According to 2021 European Prevention Guidelines Compared With Other International Guidelines,” *JAMA Cardiol*, Jul. 2022, doi: 10.1001/jamacardio.2022.1876.

[6] M. Romanens *et al.*, “Prediction of cardiovascular events with traditional risk equations and total plaque area of carotid atherosclerosis: The Arteris Cardiovascular Outcome (ARCO) cohort study,” *Prev Med (Baltim)*, vol. 147, Jun. 2021, doi: 10.1016/j.ypmed.2021.106525.

[7] M. Romanens *et al.*, “Improvement of cardiovascular risk prediction: time to review current knowledge, debates, and fundamentals on how to assess test characteristics.,” *Eur J Cardiovasc Prev Rehab*, vol. 17, no. 1, pp. 18–23, 2010.

[8] W. Herrington, B. Lacey, P. Sherliker, J. Armitage, and S. Lewington, “Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease,” *Circ Res*, vol. 118, no. 4, pp. 535–546, Feb. 2016, doi: 10.1161/CIRCRESAHA.115.307611.

[9] J. M. Tarkin *et al.*, “Imaging Atherosclerosis,” *Circ Res*, vol. 118, no. 4, p. 750, Feb. 2016, doi: 10.1161/CIRCRESAHA.115.306247.

[10] M. Romanens, I. Sudano, A. Adams, and E. A. Schober, “Sonographic assessment of carotid atherosclerosis: preferred risk indicator for future cardiovascular events?,” *Swiss Med Wkly*, vol. 149, p. w20142, 2019.

[11] U. Baber *et al.*, “Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: The bioimage study,” *J Am Coll Cardiol*, vol. 65, no. 11, pp. 1065–1074, 2015, doi: 10.1016/j.jacc.2015.01.017.

[12] H. Sillesen *et al.*, “Carotid plaque burden as a measure of subclinical atherosclerosis: Comparison with other tests for subclinical arterial disease in the high risk plaque bioimage study,” *JACC Cardiovasc Imaging*, vol. 5, no. 7, pp. 681–689, 2012, doi: 10.1016/j.jcmg.2012.03.013.

[13] C. J. Östgren *et al.*, “Systematic Coronary Risk Evaluation estimated risk and prevalent subclinical atherosclerosis in coronary and carotid arteries: A population-based cohort analysis from the Swedish Cardiopulmonary Bioimage Study,” *Eur J Prev Cardiol*, 2020, doi: 10.1177/2047487320909300.

[14] U. Baber *et al.*, “Detection and Impact of Subclinical Coronary and Carotid Atherosclerosis on Cardiovascular Risk Prediction and Reclassification in Asymptomatic Us Adults: Insights From the High Risk Plaque Bioimage Study,” *J Am Coll Cardiol*, vol. 63, p. A998, 2014.

[15] M. S. Lo-Kioeng-Shioe *et al.*, “Prognostic value of coronary artery calcium score in symptomatic individuals: A meta-analysis of 34,000 subjects,” *Int J Cardiol*, vol. 299, pp. 56–62, Jan. 2020, doi: 10.1016/j.ijcard.2019.06.003.

[16] J. M. Tarkin *et al.*, “Atherosclerosis Compendium Imaging Atherosclerosis,” 2016, doi: 10.1161/CIRCRESAHA.115.306247.

[17] A. V. Poznyak, V. N. Sukhorukov, I. I. Eremin, I. I. Nadelyaeva, and A. N. Orekhov, “Diagnostics of atherosclerosis: Overview of the existing methods,” *Frontiers in Cardiovascular Medicine*, vol. 10. Frontiers Media S.A., 2023. doi: 10.3389/fcvm.2023.1134097.

[18] A. Arbab-Zadeh and V. Fuster, “The myth of the ‘vulnerable plaque’: transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment,” *J Am Coll Cardiol*, vol. 65, no. 8, pp. 846–855, Mar. 2015, doi: 10.1016/J.JACC.2014.11.041.

[19] M. Romanens, I. Sudano, A. Adams, and W. Warmuth, “Advanced carotid atherosclerosis in middle-aged subjects: comparison with PROCAM and SCORE risk categories, the potential for reclassification and cost-efficiency of carotid ultrasound in the setting of primary care,” *Swiss Med Wkly*, vol. 149, no. 2930, 2019.

[20] M. R. Azarpazhooh *et al.*, “Reliability, reproducibility and advantages of measuring carotid total plaque area,” *Journal of the American Society of Echocardiography*, 2022, doi: 10.1016/j.echo.2021.12.016.

[21] R. C. Detrano *et al.*, “Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility--MESA study.,” *Radiology*, vol. 236, no. 2, pp. 477–484, Aug. 2005, doi: 10.1148/radiol.2362040513.

[22] A. A. Kalanuria, P. Nyquist, and G. Ling, “The prevention and regression of atherosclerotic plaques: emerging treatments.,” *Vasc Health Risk Manag*, vol. 8, pp. 549–561, 2012, doi: 10.2147/VHRM.S27764.

[23] T. Dave, J. Ezhilan, H. Vasnawala, and V. Somani, “Plaque regression and plaque stabilisation in cardiovascular diseases.,” *Indian J Endocrinol Metab*, vol. 17, no. 6, pp. 983–9, 2013, doi: 10.4103/2230-8210.122604.

[24] C. Bogiatzi and J. D. Spence, “Ezetimibe and regression of carotid atherosclerosis: importance of measuring plaque burden.,” *Stroke*, vol. 43, no. 4, pp. 1153–1155, 2012.

[25] T. Dohi *et al.*, “Plaque regression determined by intravascular ultrasound predicts long-term outcomes of patients with acute coronary syndrome.,” *J Atheroscler Thromb*, vol. 18, no. 3, pp. 231–9, 2011, doi: 10.5551/jat.6551.

[26] Y. Sato *et al.*, “Regression of an atherosclerotic coronary artery plaque demonstrated by multislice spiral computed tomography in a patient with stable angina pectoris,” *Heart Vessels*, vol. 18, no. 4, pp. 224-226 ST-Regression of an atherosclerotic cor, 2003.

[27] R. Q. Migrino, M. Bowers, L. Harmann, R. Prost, and J. F. Ladisa, “Carotid plaque regression following 6-month statin therapy assessed by 3T cardiovascular magnetic resonance: Comparison with ultrasound intima media thickness,” *Journal of Cardiovascular Magnetic Resonance*, vol. 13, no. 1, 2011, doi: 10.1186/1532-429X-13-37.

[28] C. Rusconi and R. Raddino, “Atherosclerotic Plaque Regression and Arterial Reverse Remodelling in Carotid and Femoral Arteries by Statin Use in Primary Prevention Setting : Ultrasound Findings,” in *Ultrasound Imaging - Medical Applications*, 2011.

[29] S. Rollefstad *et al.*, “Rosuvastatin-Induced Carotid Plaque Regression in Patients With Inflammatory Joint Diseases: The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study,” *Arthritis & Rheumatology*, vol. 67, no. 7, pp. 1718–1728, 2015, doi: 10.1002/art.39114.

[30] N. P. E Kadoglou, N. Sailer, A. Moumtzouoglou, A. Kapelouzou, T. Gerasimidis, and C. D. Liapis, “From the Society for Vascular Surgery Aggressive lipid-lowering is more effective than moderate lipid-lowering treatment in carotid plaque stabilization”, doi: 10.1016/j.jvs.2009.07.119.

[31] G. Di Giovanni and S. J. Nicholls, “Intensive lipid lowering agents and coronary atherosclerosis: Insights from intravascular imaging,” *Am J Prev Cardiol*, vol. 11, p. 100366, Sep. 2022, doi: 10.1016/j.ajpc.2022.100366.

[32] J. D. Spence, M. Eliasziw, M. Dicicco, D. G. Hackam, R. Galil, and T. Lohmann, “Carotid Plaque Area: a tool for targeting and evaluating vascular preventive therapy,” *Stroke*, vol. 33, no. 12, pp. 2916–2922, 2002, doi: 10.1161/01.STR.0000042207.16156.B9.

[33] M. M. J. B. M. M. R. S. B. M. F. M. C.-A. M. Rishi Trivedi, “The Agatston Coronary Artery Calcium Score in Statin Users: Recent Insights from the CAC Consortium and Pathways Forward - American College of Cardiology.” https://www.acc.org/latest-in-cardiology/articles/2021/01/19/14/27/the-agatston-coronary-artery-calcium-score-in-statin-users (accessed Aug. 20, 2022).

[34] R. Puri *et al.*, “Impact of Statins on Serial Coronary Calcification During Atheroma Progression and Regression,” *J Am Coll Cardiol*, vol. 65, no. 13, pp. 1273–1282, 2015, doi: 10.1016/j.jacc.2015.01.036.

[35] J. M. Tarkin, M. R. Dweck, and J. H. F. Rudd, “Imaging as a surrogate marker of drug efficacy in cardiovascular disease,” *Heart*, vol. 105, no. 7, pp. 567–578, Apr. 2019, doi: 10.1136/heartjnl-2017-311213.

[36] T. Dave, J. Ezhilan, H. Vasnawala, and V. Somani, “Plaque regression and plaque stabilisation in cardiovascular diseases,” *Indian J Endocrinol Metab*, vol. 17, no. 6, p. 983, 2013, doi: 10.4103/2230-8210.122604.

[37] L. P. Dawson, M. Lum, N. Nerleker, S. J. Nicholls, and J. Layland, “Coronary Atherosclerotic Plaque Regression: JACC State-of-the-Art Review,” *J Am Coll Cardiol*, vol. 79, no. 1, pp. 66–82, Jan. 2022, doi: 10.1016/J.JACC.2021.10.035.

[38] J. A. Páramo and F. Civeira, “Is regression of atherosclerotic plaque possible?,” *Clínica e Investigación en Arteriosclerosis (English Edition)* , vol. 29, no. 1, pp. 46–50, Jan. 2017, doi: 10.1016/J.ARTERE.2016.05.001.

[39] J. D. Spence, D. G. Hackam, D. Spence, D. G. Hackam, J. D. Spence, and D. G. Hackam, “Treating arteries instead of risk factors: a paradigm change in management of atherosclerosis.,” *Stroke*, vol. 41, no. 6, pp. 1193–1199, 2010, doi: 10.1161/STROKEAHA.110.577973.

[40] R. Sturlaugsdottir, T. Aspelund, S. Sigurdsson, B. Thorsson, G. Bjornsdottir, and V. Gudnason, “Cardiovascular risk factors association with total plaque area and progression in a general population: The refine-reykjavik study,” *Atherosclerosis*, vol. 241, no. 1, p. e49, Jul. 2015, doi: 10.1016/j.atherosclerosis.2015.04.176.

[41] R. Sturlaugsdottir *et al.*, “Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study,” *BMJ Open*, vol. 6, no. 11, p. e012457, 2016, doi: 10.1136/bmjopen-2016-012457.

[42] R. Sturlaugsdottir *et al.*, “Predictors of carotid plaque progression over a 4-year follow-up in the Reykjavik REFINE-study,” *Atherosclerosis*, vol. 269, pp. 57–62, 2018, doi: 10.1016/j.atherosclerosis.2017.12.005.

[43] F. Mach *et al.*, “2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk,” *Eur Heart J*, vol. 41, no. 1, pp. 111–188, 2020, doi: 10.1093/eurheartj/ehz455.

[44] P. Perrone-Filardi *et al.*, “Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Soci,” *Eur Heart J*, vol. 32, no. 16, pp. 1986–1993, 2011, doi: 10.1093/eurheartj/ehq235.

[45] J. Yeboah *et al.*, “Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals,” *JAMA*, vol. 308, no. 8, pp. 788–797, 2012, doi: 10.1001/jama.2012.9624.

[46] H. M. Den Ruijter *et al.*, “Common carotid intima-media thickness measurements in cardiovascular risk prediction: A meta-analysis,” *JAMA*, vol. 308, no. 8, pp. 796–803, 2012, doi: 10.1001/jama.2012.9630.

[47] M. Lorenz, C. Schaefer, H. Steinmetz, and M. Sitzer, “Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS).,” *Eur Heart J*, vol. 31, no. 16, pp. 2041–2048, 2010, doi: 10.1093/eurheartj/ehq189.

[48] K. P. Kim and A. J. Einstein, “Coronary artery calcification screening: estimated radiation dose and cancer risk,” *Arch Intern Med*, vol. 169, no. 13, pp. 1188–1194, 2009, doi: 10.1001/archinternmed.2009.162.

[49] M. Romanens and R. Darioli, “Risikomarker aus Bildgebungsverfahren,” in *Atherosklerose Prävention*, E. Battegy, G. Noseda, and W. Riesen, Eds., Huber Verlag, 2007. [Online]. Available: https://docfind.ch/Romanens2007.pdf

[50] M. Romanens, F. Ackermann, W. Riesen, J. D. Spence, and R. Darioli, “Imaging as a cardiovascular risk modifier in primary care patients using predictor models of the European and international atherosclerosis societies,” *Kardiovaskuläre Medizin*, vol. 10, no. 04, pp. 139–150, 2007, doi: https://doi.org/10.4414/cvm.2007.01242.

[51] E. F. Gudmundsson *et al.*, “Carotid plaque is strongly associated with coronary artery calcium and predicts incident coronary heart disease in a population-based cohort,” *Atherosclerosis*, vol. 346, pp. 117–123, Apr. 2022, doi: 10.1016/j.atherosclerosis.2022.01.018.

[52] M. B. Mortensen *et al.*, “Negative Risk Markers for Cardiovascular Events in the Elderly,” *JACC*, vol. 74, no. 1, 2019, doi: 10.1016/j.jacc.2019.04.049.

[53] E. B. Mathiesen, S. H. Johnsen, T. Wilsgaard, K. H. Bønaa, M. L. Løchen, and I. Njølstad, “Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromsø Study,” *Stroke*, vol. 42, no. 4, pp. 972–978, Apr. 2011, doi: 10.1161/STROKEAHA.110.589754.

[54] S. Harald Johnsen *et al.*, “Carotid Atherosclerosis Is a Stronger Predictor of Myocardial Infarction in Women Than in Men A 6-Year Follow-Up Study of 6226 Persons: The Tromsø Study,” 2007, doi: 10.1161/STROKEAHA.107.487264.

[55] R. Erbel *et al.*, “Diagnostic Cardiac CT for the Improvement of Cardiovascular Event Prediction,” *Dtsch Arztebl Int*, vol. 120, no. 3, pp. 25–32, Jan. 2023, doi: 10.3238/ARZTEBL.M2022.0360.

[56] M. Romanens, I. Sudano, T. Szucs, and A. Adams, “Medical costs per QALY of statins based on Swiss Medical Board assumptions,” *Cardiovasc Med*, vol. 17, no. 4, pp. 96–100, 2017.

[57] J. T. Wilkins, S. S. Gidding, and J. G. Robinson, “Can Atherosclerosis Be Cured?,” *Curr Opin Lipidol*, vol. 30, no. 6, p. 477, Dec. 2019, doi: 10.1097/MOL.0000000000000644.

[58] J. G. Robinson *et al.*, “Eradicating the burden of atherosclerotic cardiovascular disease by lowering apolipoprotein b lipoproteins earlier in life,” *J Am Heart Assoc*, vol. 7, no. 20, Oct. 2018, doi: 10.1161/JAHA.118.009778.

[59] K. J. Williams and I. Tabas, “Lipoprotein retention- and clues for atheroma regression,” *Arterioscler Thromb Vasc Biol*, vol. 25, no. 8, pp. 1536–1540, Aug. 2005, doi: 10.1161/01.ATV.0000174795.62387.D3.

[60] J. L. M. Björkegren *et al.*, “Plasma cholesterol-induced lesion networks activated before regression of early, mature, and advanced atherosclerosis,” *PLoS Genet*, vol. 10, no. 2, Feb. 2014, doi: 10.1371/JOURNAL.PGEN.1004201.

[61] D. G. Hackam and J. D. Spence, “Decline in the Severity of Carotid Atherosclerosis and Associated Risk Factors From 2002 to 2014,” *Stroke*, vol. 49, pp. 6–8, 2018, doi: 10.1161/STROKEAHA.118.021445.

[62] M. Herder, K. A. Arntzen, S. H. Johnsen, A. E. Eggen, and E. B. Mathiesen, “Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008.,” *Arterioscler Thromb Vasc Biol*, vol. 33, no. 4, pp. 858–62, 2013, doi: 10.1161/ATVBAHA.112.300767.

[63] A. Adams, W. Bojara, and M. Romanens, “Ultraschalluntersuchung der A. carotis zur verbesserten Vorhersage kardiovaskulärer Ereignisse und der Wirkung einer Statinbehandlung bei fortgeschrittener Atherosklerose,” *Herz*, Jul. 2023, doi: 10.1007/s00059-023-05197-z.

[64] P. Raggi, M. C. Gongora, A. Gopal, T. Q. Callister, M. Budoff, and L. J. Shaw, “Coronary Artery Calcium to Predict All-Cause Mortality in Elderly Men and Women,” 2008, doi: 10.1016/j.jacc.2008.04.004.

[65] J. G. Robinson *et al.*, “Eradicating the Burden of Atherosclerotic Cardiovascular Disease by Lowering Apolipoprotein B Lipoproteins Earlier in Life,” *J Am Heart Assoc*, vol. 7, no. 20, pp. 1–12, 2018, doi: 10.1161/JAHA.118.009778.

[66] M. Romanens, S. Neuner-Jehle, D. Aujesky, and R. Capaul, “Unterwandern «Querdenker» die Medizin? (mit Replik),” *Schweizerische Ärztezeitung 2021 102:22*, vol. 102, no. 22, pp. 739–740, Jun. 2021, doi: 10.4414/SAEZ.2021.19863.

[67] M. Romanens, A. Adams, W. Bojara, S. Balint, and W. Warmuth, “Cost-effectiveness analysis of statins in primary care: results from the Arteris cohort study,” *Swiss Med Wkly*, vol. 151, no. 1516, 2021, doi: 10.4414/smw.2021.20498.

[68] S. Felder, P. Jüni, C. A. Meier, and et al., “SMB Statin Recommendation,” 2014. [Online]. Available: https://www.swissmedicalboard.ch/fileadmin/public/news/2013/bericht_smb_statine_primaerpraevention_lang_2013.pdf

[69] “Stellungsnahmen zum Statinbericht des SMB,” 2014. www.medical-board.ch/fileadmin/docs/public/mb/fachberichte/ppr/2014-08-11_statine_postpubrev_anhang_definitiv.pdf

[70] M. Romanens and F. Ackermann, “SMB , AGLA und das Statin-Conundrum,” *Schweizerische Aerztezeitung*, vol. 95, no. 47, pp. 1786–1787, 2014.

[71] E. M. Gruenberg, “The Failures of Success,” *Milbank Mem Fund Q*, vol. 55, pp. 3–24, 1977.

[72] W. Baumol, D. de Ferranti, A. Pablo-Mendez, H. Tabish, and L. G. Wu, *The Cost disease. Why Computers get cheaper and Health Care Doesn’t*. 2013.

[73] H.-G. Eichler, H. Hurts, K. Broich, and G. Rasi, “Drug Regulation and Pricing — Can Regulators Influence Affordability?,” *New England Journal of Medicine*, vol. 374, pp. 1807–1809, 2016.

[74] O. Soran, A. M. Feldman, and H. A. Cohen, “Oculostenotic Reflex and Iatrogenosis Fulminans,” *Circulation*, vol. 101, pp. e198–e199, May 2000.

[75] J.-M. Gaspoz, “Smarter medicine: do physicians need political pressure to eliminate useless interventions?,” *Swiss Med Wkly*, vol. 145, p. w14125, 2015.

[76] F. Schiele and S. D. Kristensen, “The anti-statin lobby strikes again: time to set the record straight,” *Eur Heart J*, vol. 37, no. January, pp. 1–2, 2017.

[77] O. Yaqub, S. Castle-Clarke, N. Sevdalis, and J. Chataway, “Attitudes to vaccination: A critical review,” *Soc Sci Med*, vol. 112, pp. 1–11, 2014.

[78] L. P. Scheunemann and D. B. White, “The ethics and reality of rationing in medicine,” *Chest*, vol. 140, no. 6, pp. 1625–1632, 2011.

[79] A. Beresniak *et al.*, “Validation of the Underlying Assumptions of the Quality-Adjusted Life-Years Outcome: Results from the ECHOUTCOME European Project,” *Pharmacoeconomics*, vol. 33, no. 1, pp. 61–69, Jan. 2015.

[80] E. Emanuel, “Why I hope to die at 75,” *The Atlantic*, 2014. http://www.theatlantic.com/magazine/archive/2014/10/why-i-hope-to-die-at-75/379329/

[81] J. Fries, “Aging, natural death, and the compression of morbidity,” *N Engl J Med*, vol. 303, pp. 130–5, 1980.

[82] N. B. Allen *et al.*, “Favorable Cardiovascular Health, Compression of Morbidity, and Healthcare CostsClinical Perspective,” *Circulation*, vol. 135, no. 18, pp. 1693–1701, 2017.

[83] Nusselder Wilma, “Compression or expansion of morbidity?”

[84] J. F. Fries, “Aging, natural death, and the compression of morbidity,” *N Engl J Med*, vol. 303, no. 3, pp. 245–250, 1980.

[85] N. B. Allen *et al.*, “Favorable Cardiovascular Health, Compression of Morbidity, and Healthcare Costs: Forty-Year Follow-Up of the CHA Study (Chicago Heart Association Detection Project in Industry),” *Circulation*, vol. 135, no. 18, pp. 1693–1701, May 2017, doi: 10.1161/CIRCULATIONAHA.116.026252.

[86] N. B. Allen *et al.*, “Favorable Cardiovascular Health, Compression of Morbidity, and Healthcare Costs. Clinical Perspective,” *Circulation*, vol. 135, no. 18, pp. 1693–1701, 2017.

[87] M. L. Daviglus *et al.*, “Cardiovascular risk profile earlier in life and Medicare costs in the last year of life.,” *Arch Intern Med*, vol. 165, no. 9, pp. 1028–1034, May 2005, doi: 10.1001/archinte.165.9.1028.

[88] J. F. Fries, B. Bruce, and E. Chakravarty, “Compression of Morbidity 1980–2011: A Focused Review of Paradigms and Progress,” *Research Journal of Aging Research*, vol. 2011, 2011, doi: 10.4061/2011/261702.

[89] M. Romanens, A. Adams, M. Wenger, W. Warmuth, and I. Sudano, “Prognostic Impact of Carotid Plaque Imaging using Total Plaque Area added to SCORE2 in middle-aged subjects”, Accessed: Jun. 16, 2023. [Online]. Available: https://varifo.ch/wp-content/uploads/2023/06/SMW-D-22-00110_R2.pdf

[90] M. Romanens, A. Adams, I. Sudano, M. Wenger, and W. Warmuth, “Direct diagnostic and prognostic comparison of carotid plaques (Total Plaque Area) with coronary calcifications (Agatston Score).” Accessed: Jun. 16, 2023. [Online]. Available: https://varifo.ch/wp-content/uploads/2023/06/SGK2013_Romanens-Michel_Direct-diagnostic-and-prognostic-comparison-of-carotid-plaques-Total-Plaque-Area-with-coronary-calcifications-Agatston-Score.pdf

[91] J. D. Spence, “Coronary calcium is not all we need: Carotid plaque burden measured by ultrasound is better.,” *Atherosclerosis*, vol. 0, no. 0, Apr. 2019, doi: 10.1016/j.atherosclerosis.2019.04.214.

[92] J. D. Spence, “Assessment of atherosclerosis: should coronary calcium score and intima-media thickness be replaced by ultrasound measurement of carotid plaque burden and vessel wall volume?,” *Curr Opin Lipidol*, vol. 34, no. 3, pp. 126–132, Jun. 2023, doi: 10.1097/MOL.0000000000000880.

[93] J. David Spence, F. Author, M. Reza Azarpazhooh, and E. J. Mathiesen Tatjana Rundek Michel Romanens Ansgar Adams Luis Jose Armando Hernan Perez Hugo Villafañe Nestor Garcia Borja Ibañez Chrysi Bogiatzi Reza Tabrizi Valentin Fuster David Spence, “Advantages of Carotid Plaque Burden vs. Coronary Calcium in Cardiovascular Prevention: Opinion and Supporting Evidence.” Accessed: Jun. 17, 2023. [Online]. Available: https://varifo.ch/wp-content/uploads/2023/06/Submission-2022-Dec-12-EHJCI-S-22-01907-Spence.pdf

[94] A. D. Gepner *et al.*, “A Comparison of Coronary Artery Calcium Presence, Carotid Plaque Presence, and Carotid Intima-Media Thickness for Cardiovascular Disease Prediction in the Multi-Ethnic Study of Atherosclerosis (MESA),” *Circ Cardiovasc Imaging*, vol. 8, no. 1, pp. 1–8, 2015, doi: 10.1016/j.ajo.2009.07.014.Aqueous.

[95] P. A. Barnett, J. D. Spence, S. B. Manuck, and J. R. Jennings, “Psychological stress and the progression of carotid artery disease.,” *J Hypertens*, vol. 15, no. 1, pp. 49–55, 1997.

[96] P. J. Touboul *et al.*, “Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011),” *Cerebrovascular Diseases*, vol. 34, no. 4, pp. 290–296, 2012, doi: 10.1159/000343145.

[97] N. Handa *et al.*, “Ultrasonic evaluation of early carotid atherosclerosis,” *Stroke*, vol. 21, no. 11, pp. 1567–1572, 1990, doi: 10.1161/01.STR.21.11.1567.

[98] J. F. Polak *et al.*, “The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis.,” *J Am Heart Assoc*, vol. 2, no. 2, p. e000087, Jan. 2013, doi: 10.1161/JAHA.113.000087.

[99] S. Prabhakaran, R. Singh, X. Zhou, R. Ramas, R. L. Sacco, and T. Rundek, “Presence of calcified carotid plaque predicts vascular events: The Northern Manhattan Study,” *Atherosclerosis*, vol. 195, no. 1, pp. e197-201, 2007, doi: 10.1016/j.atherosclerosis.2007.03.044.

[100] V. Nambi *et al.*, “Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study.,” *JACC*, vol. 55, no. 15, pp. 1600–1607, 2010.
[101] S. A. E. Peters *et al.*, “The Use of Plaque Score Measurements to Assess Changes in Atherosclerotic Plaque Burden Induced by Lipid-Lowering Therapy Over Time: The METEOR Study.,” *J Atheroscler Thromb*, vol. 18, no. 9, pp. 784–795, 2011, doi: 10.5551/jat.8169.
[102] M. Plichart *et al.*, “Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study.,” *Atherosclerosis*, vol. 219, no. 2, pp. 917–24, 2011, doi: 10.1016/j.atherosclerosis.2011.09.024.
[103] T. Rundek, H. Arif, B. Boden-Albala, M. S. Elkind, M. C. Paik, and R. L. Sacco, “Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study.,” *Neurology*, vol. 70, no. 14, pp. 1200–1207, 2008, doi: 10.1212/01.wnl.0000303969.63165.34.
[104] S. Coli *et al.*, “Contrast-Enhanced Ultrasound Imaging of Intraplaque Neovascularization in Carotid Arteries,” *J Am Coll Cardiol*, vol. 52, no. 3, pp. 223–230, 2008, doi: 10.1016/j.jacc.2008.02.082.