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Roadmap

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Roadmap on the use of artificial intelligence for imaging of vulnerable atherosclerotic plaque in coronary arteries

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Abstract

Artificial intelligence (AI) is likely to revolutionize the way medical images are analysed and has the potential to improve the identification and analysis of vulnerable or high-risk atherosclerotic plaques in coronary arteries, leading to advances in the treatment of coronary artery disease. However, coronary plaque analysis is challenging owing to cardiac and respiratory motion, as well as the small size of cardiovascular structures. Moreover, the analysis of coronary imaging data is time-consuming, can be performed only by clinicians with dedicated cardiovascular imaging training, and is subject to considerable interreader and intrareader variability. AI has the potential to improve the assessment of images of vulnerable plaque in coronary arteries, but requires robust development, testing and validation. Combining human expertise with AI might facilitate the reliable and valid interpretation of images obtained using CT, MRI, PET, intravascular ultrasonography and optical coherence tomography. In this Roadmap, we review existing evidence on the application of AI to the imaging of vulnerable plaque in coronary arteries and provide consensus recommendations developed by an interdisciplinary group of experts on AI and non-invasive and invasive coronary imaging. We also outline future requirements of AI technology to address bias, uncertainty, explainability and generalizability, which are all essential for the acceptance of AI and its clinical utility in handling the anticipated growing volume of coronary imaging procedures.

Sections

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Key points

- Artificial intelligence (AI) might have the potential to transform the assessment of vulnerable or high-risk plaque in coronary arteries by improving the detection, quantification and prognostication of vulnerable plaque and integration with other imaging and clinical parameters.
- The advantages of AI for the assessment of vulnerable plaque images include reducing observer variability, improving accuracy, enabling standardization, improving speed and facilitating the synthesis of diverse information.
- The challenges for the development and implementation of AI include the presence of anatomical variations and imaging artefacts; the lack of reproducibility, generalizability and robustness across diverse imaging platforms; and the potential for the technology to introduce or worsen biases.
- Clinical research has already been performed on AI tools for plaque assessment, but validated commercial solutions for clinical use are not yet available.
- For AI to achieve its true potential for vulnerable plaque assessment in clinical practice, large and diverse studies are required, and AI tools must be trustworthy, explainable and interpretable.

Introduction

Initially perceived with scepticism, artificial intelligence (AI; Fig. 1) is now a part of our everyday lives. A case in point is AI-based, automated speech and facial recognition, which was believed not to be possible in the 1960s, but is now available on many smartphones[1]. In the past decade, AI-based methods have been increasingly used in cardiovascular medicine, especially in cardiovascular imaging[2–5]. The majority of these AI methods have been developed for the diagnosis, risk stratification and prognostic assessment of patients with coronary artery disease, heart failure or rhythm disorders[6]. The evidence on the prognostic implications of a vulnerable atherosclerotic plaque in coronary arteries, which is considered to precede acute coronary events through plaque rupture and subsequent thrombosis[7], has become more robust in the past 10 years[8–10]. Accurate non-invasive or invasive imaging approaches that can identify patients at high risk of adverse events might help to guide focal strategies or intensified medical treatment. However, visual and especially quantitative coronary plaque detection and characterization are time-consuming, require a high level of expertise, and have substantial intraobserver and interobserver variability[11,12].

Among non-invasive imaging modalities, coronary CT angiography (CCTA) is the best for visualizing coronary arteries and atherosclerotic plaques[13]. AI technologies have also been implemented in the analysis of images derived from invasive intravascular ultrasonography (IVUS) or optical coherence tomography (OCT)[13]. Research that initially focused on (semi-)automated lumen detection for stenosis grading[14] has now moved on to the promising field of automated plaque characterization[15,16].

In this Roadmap, we review the existing evidence on and provide interdisciplinary consensus recommendations for the application of AI to the imaging of atherosclerotic plaque in coronary arteries, focusing on the most advanced imaging modalities in this field (CCTA, IVUS and OCT[13]). In addition, we discuss the current and future approaches to addressing bias, explainability, uncertainty and generalizability of AI-guided imaging of coronary plaque. Consensus was reached using a Delphi methodology similar to that used to reach a consensus on myocardial ischaemia imaging at the first Quantitative Cardiovascular Imaging (QCI) meeting[17]. Detailed clinical consensus recommendations on the preferred use of each imaging technique for coronary plaque and stenosis imaging in specific patient populations are provided in a Consensus Statement derived from the second QCI meeting[13].

Methodology for consensus recommendations

The application of AI to cardiovascular imaging has received increasing interest over the past 10 years[18]. However, many technical and clinical aspects of its application to the imaging of vulnerable plaques in coronary arteries require additional attention to ensure reliability and to improve the prognostic and diagnostic value of different cardiovascular imaging modalities before widespread clinical use. During the second QCI meeting on coronary artery stenosis and atherosclerosis imaging in September 2022, a questionnaire regarding the clinical appropriateness of different imaging modalities was conducted using a three-round Delphi method. This Roadmap describes the findings that have emerged using this multidisciplinary approach and encompasses the views of clinicians (cardiologists, radiologists and a cardiac surgeon), biomedical engineers and computer scientists using a similar method to that used for the first QCI meeting[17]. The questionnaire included eight questions on AI for coronary imaging, and no consensus was noted after the third and final round of questions (Supplementary Table 1), which led to a second Delphi process with two additional rounds needed to reach a consensus[19,20]. The questions were sent to 14 scientists and physicians directly involved in the research and development of AI tools for cardiovascular imaging. A total of 15 questions (Supplementary Table 2) were answered using a Likert scale from 1 to 9, categorical replies or free text. The reasoning for each answer was provided as text. Before beginning the second round, the overall results from the first round were sent to the participants. The questions answered using a Likert scale were presented as a median and interquartile range, the categorical replies were presented as percentages, and the relevant or conflicting replies in the text were highlighted. The final results of the Delphi voting are summarized in Table 1, with a level of consensus between experts indicated as no consensus, partial consensus or consensus. The level of consensus for answers in the form of the Likert scale or ordinal scale was defined using previously proposed parameters (<0.6 indicated no consensus, 0.6–0.8 indicated partial consensus and ≥0.8 indicated consensus)[21]. For answers on ordinal scales and related to multiple modalities, the measure of agreement was averaged across all modalities. For answers on a nominal scale, consensus was measured using normalized entropy with the same thresholds.

The concept of vulnerable plaque imaging

In most patients, acute coronary syndrome is triggered by the rupture or erosion of coronary atherosclerotic plaques[22]. These plaques have specific features, such as a large necrotic core and a thin fibrous cap, known as a thin-cap fibroatheroma (TCFA). The identification of these features, which can be visualized using imaging modalities, led to the concept of the vulnerable plaque that is prone to rupture (Fig. 2). Many clinical studies using invasive and non-invasive techniques have found an association between vulnerable plaques and adverse outcomes in patients[13,23]. However, findings from both pathology and clinical imaging studies have also consistently shown that the rupture of these vulnerable plaques often occurs without clinical syndromes, representing an integral part of plaque progression[24]. Furthermore, although stenting of lesions with vulnerable plaque features is safe[25], there is currently a paucity of data supporting focal treatment of vulnerable plaques. Therefore, the concept of the vulnerable plaque remains controversial[13,23]. The clinical implications of quantitative non-invasive and invasive imaging of vulnerable plaques in coronary arteries have also been described in a consensus statement derived from findings from the second QCI meeting on clinical quantitative coronary artery stenosis and coronary atherosclerosis imaging[13]. Further characterization of coronary atherosclerosis using AI might result in the identification of additional features associated with rapid plaque progression and increased risk of adverse events.

Imaging modalities

Coronary atherosclerotic plaque can be assessed by a range of invasive and non-invasive imaging modalities[13]. CT and MRI facilitate non-invasive structural imaging of coronary plaque, whereas X-ray coronary angiography, IVUS, OCT and NIRS are invasive imaging techniques that can be used to assess coronary artery morphology. Although OCT and IVUS are superior to CT in terms of resolution, these invasive modalities are not widely available[13]. Beyond anatomical imaging, coronary plaque biology can be assessed non-invasively through the use of appropriately targeted radiotracers. Only PET, which again is not widely available, allows the assessment of coronary atherosclerotic plaque biology via radiotracer uptake[26].

Non-invasive plaque imaging. CCTA is a non-invasive imaging modality that facilitates the identification of qualitative high-risk plaque features, such as the napkin-ring sign, and the quantification of total plaque burden using CCTA[27] correlates well with assessment by IVUS[28,29]. Moreover, the CCTA-derived measure of plaque attenuation can be used to determine plaque composition, including total, calcified, non-calcified or low attenuation plaque (Fig. 2). Low attenuation plaque is of particular interest because it correlates with the lipid-rich necrotic core of atheromatous plaques and has been associated with adverse outcomes[8]. Importantly, CT quantification of coronary atherosclerotic burden can be used to predict the risk of fatal or non-fatal myocardial infarction in patients with stable or unstable coronary artery disease[8,27,30,31]. Of note, however, CCTA is associated with exposure to a modest level of radiation, and image quality can be compromised by cardiac motion or coronary calcification.

Invasive plaque imaging. Coronary X-ray angiography is the most frequently used invasive modality for imaging the coronary arteries because it allows excellent visualization of the coronary lumen, but not of coronary plaque. Therefore, invasive assessment of coronary plaque requires intravascular imaging techniques such as IVUS, OCT and NIRS[9,32]. Specifically, plaque imaging using IVUS or OCT is instrumental for studying vulnerable plaque features[33], and has been used to guide percutaneous coronary interventions[33,34] and to monitor vascular tissue response[35,36]. OCT is currently the only imaging modality with sufficient spatial resolution to identify the thin cap (<0.065 mm) that defines true TCFA. Of note, these non-invasive techniques cannot be used to assess severe stenotic disease, small-calibre vessels or deeper plaque structures. Of note, intracoronary imaging is expensive, can cause serious complications because of its invasive nature and is, therefore, impractical for population-wide application.

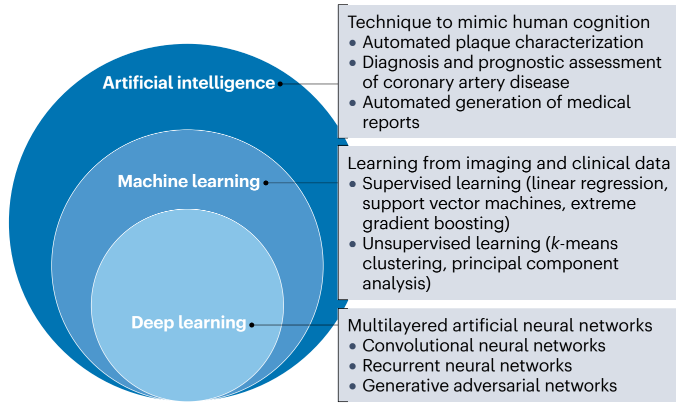

Fig. 1 | Basics of artificial intelligence, machine learning and deep learning. Artificial intelligence in medicine mimics the intelligence of a human in performing various medical tasks. Machine learning is a subfield of artificial intelligence with a focus on how computers learn from examples. Deep learning is a specific form of machine learning involving an algorithm that learns directly from data[48].

Prognostic value of identifying vulnerable plaques

The prognostic importance of coronary plaque assessment has been established using various non-invasive and invasive imaging modalities. TCFA, identified using IVUS or OCT, has been associated with worse outcomes in several prospective studies[9,37–39]. Vulnerable plaques that can be visually identified on CCTA have been linked to an increased risk of subsequent adverse cardiac events in registry studies[40] and in randomized controlled trials (RCTs)[8,31,41]. In the PROMISE trial[31], vulnerable plaques were present in 15% of patients presenting with suspected coronary artery disease and were associated with an almost twofold increase in major adverse cardiovascular events, after adjusting for cardiovascular risk factors. However, this study did not adjust for the overall disease burden. In addition, findings from studies that quantitatively assessed vulnerable plaques suggest that increased plaque volume and imaging markers of TCFA are associated with a higher risk of subsequent adverse cardiac events. In the PROSPECT study[9], a plaque burden of ≥70% and a minimal lumen area of ≤4.0 mm^2, as measured on IVUS, were independently associated with disease progression and recurrent chest pain at follow-up in patients presenting with acute coronary syndrome. In the SCOT-HEART trial[27], a low attenuation plaque burden on CCTA was a strong predictor of myocardial infarction, over and above the cardiovascular risk score, calcium score and presence of stenosis. Patients with a low attenuation plaque burden of >4% were nearly five times more likely to have a subsequent myocardial infarction event than patients who had a low attenuation plaque burden of ≤4%. Conversely, preliminary results from the ISCHEMIA trial[42] did not find low attenuation plaque to be predictive of death or myocardial infarction when adjusted for total plaque burden. Importantly, the positive predictive value of vulnerable plaque features is low, and it is not possible at present to predict which patients will have plaque progression that would ultimately cause major adverse cardiovascular events. Larger studies and the incorporation of AI technology will hopefully improve the assessment of vulnerable plaque in the future[43,44]. Aside from traditional high-risk plaque features, AI technology can support the automatic identification of additional high-risk plaque features that are not visible to the human eye to improve diagnosis and prognosis.

Table 1 | Consensus recommendations on AI applied to imaging of vulnerable plaques in coronary arteries

Question	Level of consensus[a]	Consensus recommendations
Current state of AI for analysis of plaques in coronary arteries		
Q1: reference standard for plaque imaging	Consensus	Histology would be preferable but clinically impractical; IVUS and OCT are superior to CT with regard to resolution but availability is limited; OCT is more precise than IVUS and can detect high-risk plaque features associated with plaque progression
Q2a: importance of multiple observers	Partial consensus	Multiple observers are essential to compensate for interobserver variability, provide generalizability and help with uncertainty estimation
Q2b: required level of expertise for annotation of plaques	Partial consensus	The number of analysed scans and years of experience should both be considered; the number of expected analysed scans varied from 100 to >1,000; the number of years of experience ranged from 24 weeks to 5 years; and certifications of cardiovascular CT experience (such as SCCT level III) might be sufficient
Q3: availability of AI tools for automated plaque analysis in academic research	Partial consensus	AI tools exist for all modalities, with more tools available for CT; however, access to research tools is limited
Q4: availability of FDA-approved or CE-approved AI tools for automated plaque analysis in clinical practice	No consensus	Large discrepancies in the definition of AI tools led to discordance between experts; the technologies used (such as simple thresholding or deep learning) are mostly hidden from the user, making it difficult to define AI tools
Current challenges with AI in automated plaque analysis and prognosis		
Q5: quality level of current automated vessel wall and lumen segmentation for coronary plaque analysis	Consensus	No standardization on how to quantify plaque burden is available at present; most of the available tools are challenged by the presence of artefacts and severe calcifications; CT is limited in the case of heavy calcification; data interpretation is subjective with a paucity of quantification, and segmentations are sparse and noisy; and OCT is more advanced than IVUS in AI segmentation, especially in the case of insufficient image quality (such as blood artefacts)
Q6: susceptibility of AI tools for plaque analysis to image artefacts	Partial consensus	Current AI tools are highly susceptible to image artefacts and most AI tools do not account for them
Q7: technology suited for classification of coronary plaques into stable and vulnerable plaques	Partial consensus	A combination of radiomics and deep learning provides incremental utility compared with either method alone; deep learning might be superior to radiomics, but requires more data, which are not currently available
Trustworthy AI		
Q8: mandatory visual confirmation of automated segmentation of plaques	Consensus	Visual confirmation is required until full confidence is achieved; physicians need to be able to modify or correct coronary segmentations
Q9: requirement for randomized controlled trials	No consensus	Randomized controlled trials are required to verify clinical effectiveness and test advantages over standard care, whereas retrospective studies are sufficient if AI tools only facilitate simple human tasks (such as image segmentation)
Q10: confidence measure to explain uncertainty	Partial consensus	Well-calibrated and reliable quantitative measures are required (such as with 95% confidence interval); visual methods (such as heatmaps) are required to ensure clarity in interpretation; and low confidence should alert physicians that further testing might be required
Q11: bias mitigation	Partial consensus	AI tools should be developed and tested on large and diverse populations to ensure their generalizability; the limitations of AI tools with respect to non-representative populations should be clearly demonstrated; biases should be evaluated and quantified; and bias in datasets should be mitigated by adding or upweighting minority samples when possible
Outlook and future directions		
Q12: reading time of an imaging test in clinical practice	Consensus	Images are quickly screened in clinical practice (5–10 min) without measuring plaque features, whereas detailed plaque analysis can take >1 h; reading time highly depends on the complexity of the case
Q13: AI-supported time savings	Consensus	Quantitative plaque assessment is not performed regularly in current clinical practice; AI tools could provide full quantification without changing reading time; and higher accuracy and reproducibility are important advantages in addition to time savings
Q14: on-site or cloud-based plaque analysis	Consensus	Issues of data protection and data privacy preservation must be addressed before cloud-based solutions can be used; OCT and IVUS require immediate assessment (real-time systems) to guide decision-making
Q15: automated generation of structured medical reports	Consensus	Structured reports should provide treatment recommendations together with explanations and should include a breakdown of findings (plaque burden and subtypes) and quantitative measurements with a summary; the ability to add user-defined free text is also required

AI, artificial intelligence; IVUS, intravascular ultrasonography; OCT, optical coherence tomography; SCCT, Society of Cardiovascular Computed Tomography. [a]The level of consensus between experts is graded as no consensus, partial consensus or consensus. The full questionnaire with individual responses is shown in Supplementary Table 2.

AI for vulnerable plaque assessment

AI is a branch of computer science that aims to mimic human cognition in performing tasks such as object or pattern recognition and has been applied to the field of medical imaging[45]. Machine learning, a subfield of AI, enables computer algorithms to automatically learn and improve from experience using supervised or unsupervised learning. Deep learning is a specific form of machine learning that uses multilayered artificial neural networks to make predictions directly from input (Fig. 1). Unlike traditional machine learning techniques, deep learning has emerged in the field of cardiovascular imaging only in the past 7 years[46], but has already accelerated research on the assessment of vulnerable plaques and on prerequisite tasks such as lumen and plaque segmentation[46,47]. The most commonly used deep learning networks for image analysis are convolutional neural networks (CNNs). CNNs contain many layers, including one or more convolutional layers that create a feature map summarizing the presence of detected features in the input. The most common implementation of CNNs allows image segmentation or image classification. Although the success of deep learning depends on the availability of large datasets, standard models, such as U-Net and convolutional Long Short-Term Memory networks, as well as specialized networks have been applied to vulnerable plaque segmentation[47]. In addition, radiomics is a technique involving the extraction of a large number of quantitative features (such as shape, texture and grey-level statistics) that are often not visible to the human eye to describe texture and spatial complexity. Machine learning methods are used to perform precision phenotyping and can build predictive models on the basis of radiomic patterns. Radiomics can be used to identify high-risk plaque features, characterize plaque vulnerability[48,49] and find associations that are predictive of an increased risk of major adverse cardiovascular events[50].

AI technology allows the quantitative assessment of coronary plaque and the identification of adverse plaque characteristics in the coronary arteries. Automatically quantified biomarkers (Fig. 3) can improve diagnosis and facilitate patient-specific cardiovascular risk stratification[27,51]. Relevant studies that have assessed the prognostic value of vulnerable plaque and their level of automation using AI are listed in Supplementary Table 3.

Non-invasive assessment

CCTA is a first-line non-invasive test for assessing patients with suspected coronary artery disease[52]. Visual or semi-automatic analysis of CCTA focuses on grading stenosis severity and assessing basic plaque features. AI-based methods can automate not only these time-consuming and cumbersome quantification tasks, but also the characterization of coronary artery plaque and stenosis grading[46] (Fig. 3).

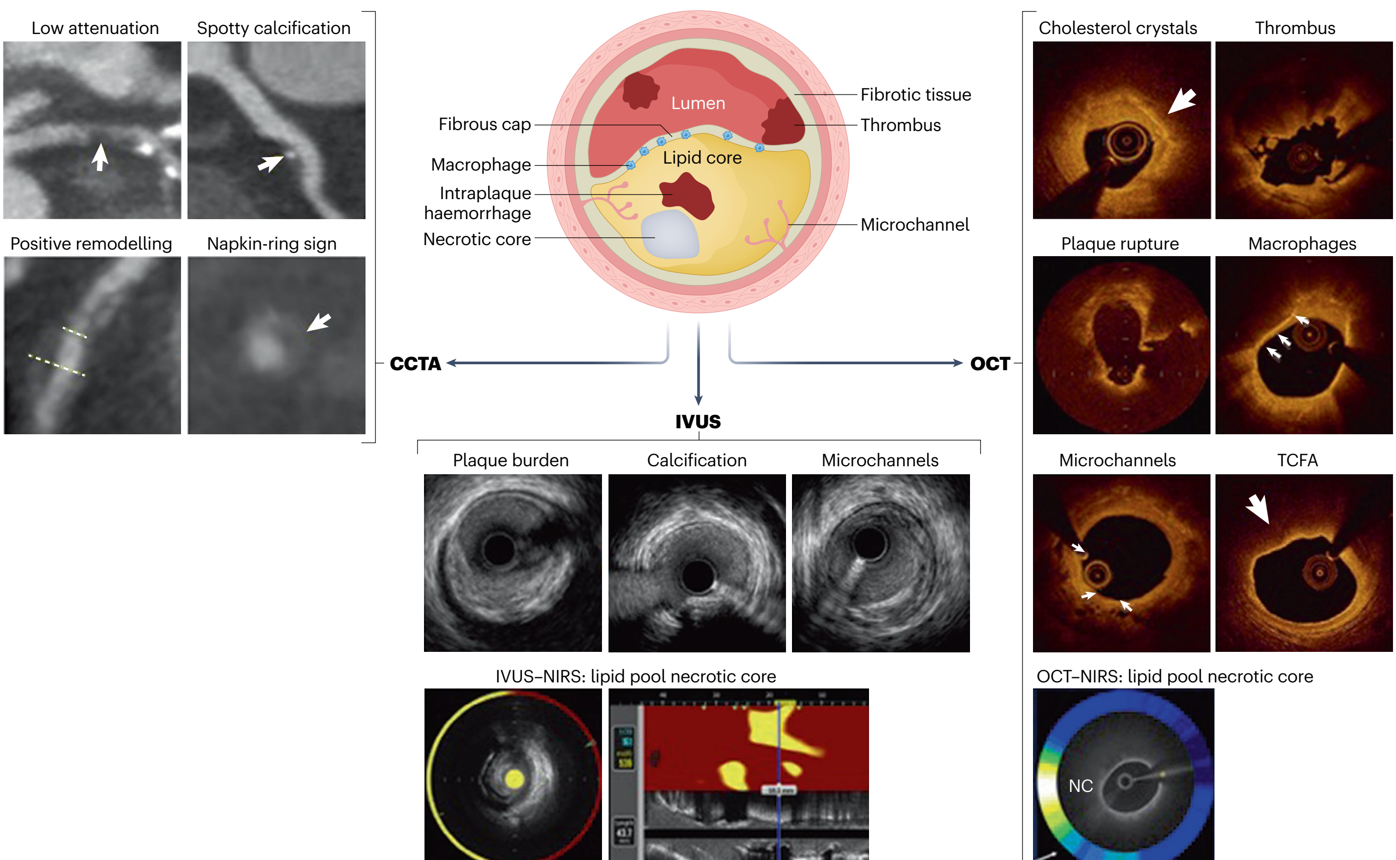

Fig. 2 | The concept of vulnerable plaques and high-risk plaque features in CCTA, IVUS and OCT images. The figure provides an overview of vulnerable plaque components (lipid core, necrotic core and thin fibrous cap) and associated high-risk plaque features in coronary CT angiography (CCTA; the arrows point to low attenuation, spotty calcification and napkin-ring sign, whereas the dashed lines indicate positive remodelling), intravascular ultrasonography (IVUS; plaque burden, calcification and microchannels) and optical coherence tomography (OCT; the large arrows point to cholesterol crystals and thin-cap fibroatheroma (TCFA), whereas the small arrows indicate macrophages and microchannels). NC, necrotic core; NIRS, near-infrared spectroscopy.

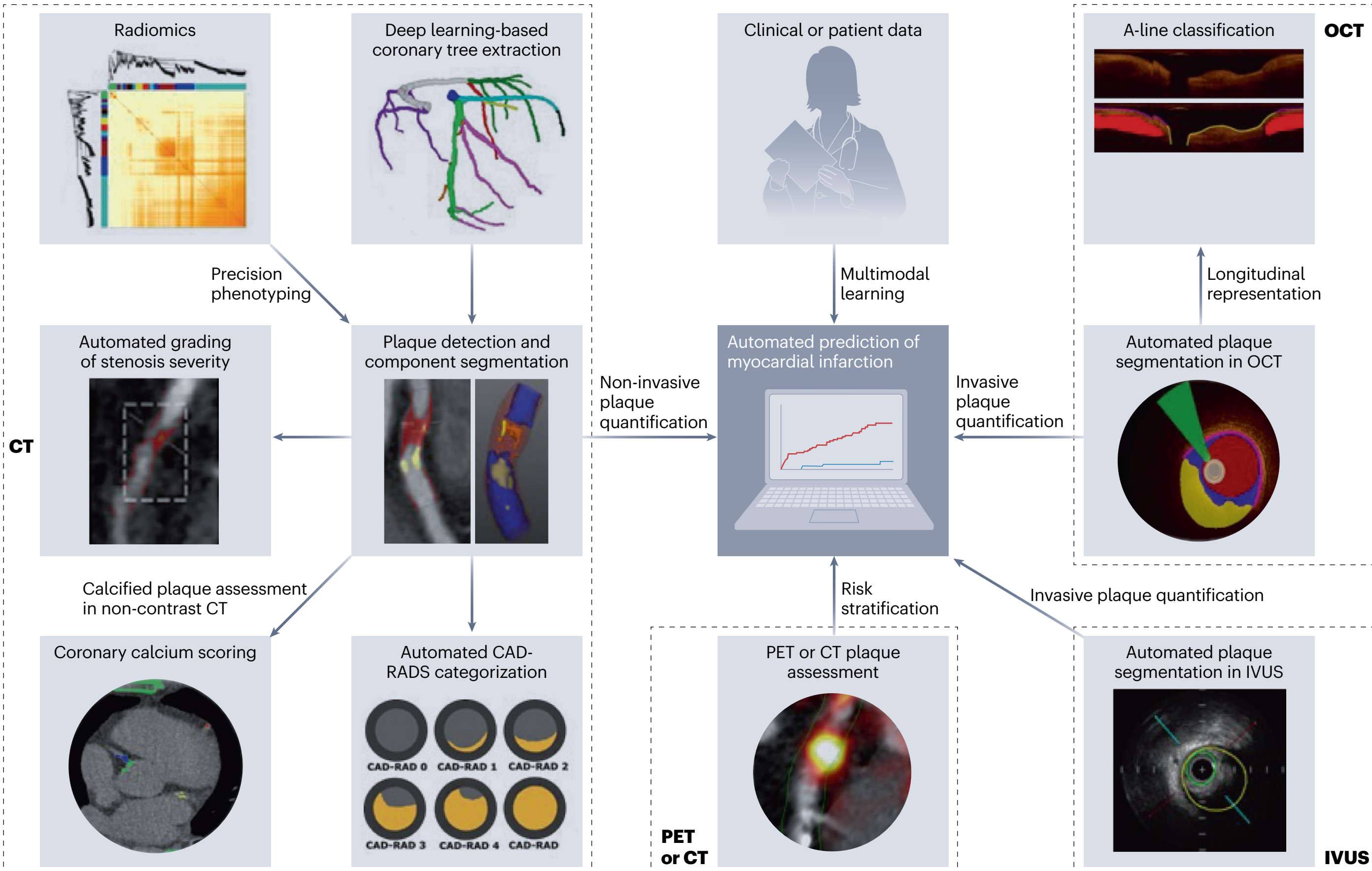

Fig. 3 | The interaction between tasks supported by AI tools for the assessment of vulnerable plaques in coronary arteries. The figure summarizes the tools for the assessment of vulnerable plaques supported by artificial intelligence (AI) in CT, intravascular ultrasonography (IVUS) and optical coherence tomography (OCT). AI-supported tasks include segmentation (coronary tree extraction, calcium scoring and plaque segmentation), feature extraction (radiomics, PET or CT plaque assessment and stenosis grading), classification tasks (Coronary Artery Disease Reporting and Data System (CAD-RADS) categorization[120] and multimodal learning), risk stratification and prediction of major adverse cardiovascular events.

Automated coronary artery calcium scoring. Automated quantification of coronary artery calcification in non-contrast CT[53] and low-dose chest CT[54] shows excellent agreement with non-automated human quantification in terms of risk stratification. Automated quantification of coronary artery calcification identified on CCTA has good accuracy compared with non-automated quantification of the traditional Agatston scores derived from non-contrast CT[55,56].

Centreline extraction. Methods that detect both calcified and non-calcified plaque and stenosis usually require the generation of a coronary artery centreline to facilitate analysis of the artery and its immediate vicinity[46]. Therefore, a number of automatic or semi-automatic methods have been developed for coronary artery tree extraction, plaque segmentation and stenosis grading using conventional machine learning or deep learning techniques[46,48,57].

Identification of vulnerable plaque characteristics. Aside from quantifying plaque burden, AI-based methods have also been used to identify vulnerable plaque characteristics, such as positive remodelling, low attenuation plaque, spotty calcification and the napkin-ring sign[48,58].

Radiomics can extract a large number of quantitative features, most of which are invisible to the human eye, from medical images (Fig. 3). These features capture the complex spatial relationships between voxels by describing textural patterns or geometric properties within a given imaging region of interest, such as a segmented coronary plaque. CCTA-based radiomics have been used to improve the identification of the napkin-ring sign[58] and other vulnerable plaque characteristics[59]. In this context, machine learning techniques have resulted in the identification of imaging biomarkers associated with culprit lesions in acute coronary syndrome[60].

Multimodal plaque assessment. In cardiovascular imaging, AI algorithms can be used both to quantify new imaging biomarkers and to integrate data from many different sources for comprehensive, patient-tailored risk prediction (Fig. 3). For example, in a machine learning analysis of findings from a multicentre prospective registry, the combination of patient, clinical and plaque characteristics using an iterative LogitBoost algorithm was found to predict 5-year all-cause mortality more accurately than using existing clinical or CCTA metrics alone[53]. Another study combined qualitative and quantitative plaque features in XGBoost models to identify precursors of culprit lesions in patients with acute coronary syndrome; this boosted ensemble algorithm outperformed the use of traditional metrics of diameter stenosis, CCTA-related high-risk plaque features and lesion-level characteristics in the detection of culprit lesions[61]. Furthermore, several studies have used machine learning to combine plaque characteristics, including size, geometry and density, to identify myocardial ischaemia[62–65]. Investigators in a multicentre trial involving 254 patients combined clinical data with quantitative and qualitative plaque characteristics using a LogitBoost algorithm to detect lesion-specific ischaemia that was defined by invasive fractional flow reserve[66]. This approach predicted the presence of lesion-specific ischaemia (area under the receiver operating characteristic curve (AUC) 0.84) more accurately than parameters such as quantitative stenosis (AUC 0.76), total plaque volume (AUC 0.74) and pre-test likelihood of coronary artery disease (AUC 0.63), highlighting the usefulness of analysing detailed plaque characteristics.

AI has been used to improve cardiovascular risk prediction by integrating complex clinical data with multimodality coronary plaque data[67]. One study showed that machine learning by extreme gradient boosting using clinical data, quantitative CCTA plaque analysis and measures of coronary plaque activity from ^{18}F-sodium fluoride (^{18}F-NaF) PET could predict adverse clinical outcomes in patients with established coronary artery disease[68]. The investigators demonstrated that the AI model that best predicted myocardial infarction (AUC 0.85) combined clinical data with both quantitative measures of anatomical coronary plaque from CCTA and coronary disease activity from ^{18}F-NaF PET[68].

Investigators in an international multicentre study involving 921 patients undergoing CCTA developed and validated a deep learning system for CCTA-derived measures of plaque volume and stenosis severity[47]. The deep learning convolutional network was trained to segment plaques in all patients and then validated in a test set involving >200 patients, including 50 patients undergoing coronary IVUS within 1 month of CCTA. The deep learning system completed plaque analysis in less time than expert readers (5.7 s versus 25.7 min), with good or excellent agreement between the two sets of measurements[47]. There was also excellent agreement between the deep learning-derived measurements and the expert-derived measurements with regard to IVUS for total plaque volume and minimal luminal area, as well as in the assignment of patients to categories of stenosis severity[69]. The investigators further validated the capacity of deep learning-based plaque quantification to predict cardiovascular outcomes in another external cohort of 1,611 patients from the SCOT-HEART trial[47]. A deep learning-based total plaque volume of ≥238 mm^3 was associated with a fivefold higher risk of myocardial infarction, adding prognostic value to the presence of obstructive stenosis and the clinical risk score.

Invasive assessment

Manual expert quantification of plaque burden and vulnerable plaque characteristics (Fig. 2), such as measuring lipid arcs and minimal fibrous cap thickness in images derived from OCT and IVUS, is very time-consuming and requires real-time decision-making (Table 1). The use of AI technology can improve the efficiency and accuracy of these processes.

Automatic segmentation in OCT. To date, automation of the quantification and characterization of atherosclerotic plaque is mostly restricted to automatic segmentation. Deep learning approaches allow accurate and very fast segmentation in a matter of milliseconds[15]. These technologies relieve human experts of repetitive tasks and allow real-time analysis, which is crucial in intravascular imaging. Moreover, experts have an opportunity to understand what segmentation the AI model has performed, which improves trust and user acceptance (Table 1).

A-line-based classification. For A-line-based classification[70–72], the cross-sectional view is rearranged longitudinally and plaques are subsequently classified circumferentially on each A-line. These algorithms use the natural direction of light emitted by the OCT catheter and are independent of the indeterminable external elastic membrane resulting from complete light attenuation in lipid plaques (Fig. 2). This technique also allows fibrous cap detection and quantification after manual adjustment in 5.5% of frames[73].

Pixel-based deep learning. Conversely, pixel-based deep learning algorithms allow the segmentation of individual plaque components on cross-sectional views and can incorporate 3D spatial information, which is fundamental for intravascular image analysis. Investigators have developed a U-shaped neural network that automatically segments a single OCT frame in 0.07 ± 0.01 s with a mean Dice similarity coefficient of 0.764, which had lower accuracy for high-risk plaque components (such as macrophage accumulation) than for plaque segmentation[15]. In this study, the overall diagnostic accuracy for region segmentation and characterization of the external validation cohort was 86.6%[15]. A pixel-based approach using CNNs developed by another group of investigators resulted in sensitivities and specificities of >85% for the identification of lipid and calcified plaques[74]. Classification can also be performed in a binary per-frame fashion (for example, for TCFA identification)[75,76]. In a study that assessed the utility of a DenseNet model to classify frames with OCT-derived TCFA, the deep learning algorithm accurately detected an OCT-derived TCFA with high reproducibility in their internal validation set of almost 10,000 frames (AUC 0.96)[75]. However, the percentage of false-positive classifications was 6% at the frame level and 31% at the vessel level. The time required to analyse a pullback was only 2.1 ± 0.3 s compared with 289 ± 270 s for manual assessment. Interestingly, the results of histology-based training in addition to OCT-based training were found to be superior to OCT-based training only[77].

Automated segmentation in IVUS. Image-based approaches in IVUS are limited by low spatial resolution. Consequently, most algorithms use binary per-frame or circumferential plaque segmentation[16,78]. Deep learning-based plaque analysis with feature extraction has led to promising results for the identification of TCFA (AUC 0.84–0.91), with OCT as the gold standard[78]. Furthermore, in another study, the Dice similarity coefficients for the identification of calcified plaque and attenuation were 0.79 and 0.74 at the angle-level, respectively, after degree-wise learning[16].

Availability of AI tools

Although numerous AI methods for the assessment of coronary artery plaques have been developed and used in research, they are not widely available for clinical use (Table 2). Published scientific papers often do not provided access to the source code, data or trained models in public repositories, which prevents reproducibility analysis. The QCI expert group reached a partial consensus on the current state of the availability of AI tools for plaque assessment in academic research.

Table 2 | Relevant AI tools for plaque imaging in research and clinical practice

Modality	Device or software	Manufacturer	Approval pathway	Approval number	AI support	Intended use	Refs.
CT	vascuCAP	Elucid Bioimaging	FDA 510(k) 2017; CE mark October 2017	K183012	Fully 3D segmentations of lumen, wall and each tissue type on CCTA	Not intended to provide a diagnosis, but intended to assist trained physicians with patients who have been identified as having atherosclerosis	103–105
	cvi42 Auto Imaging Software Application	Circle Cardiovascular Imaging	FDA 510(k) July 2022; CE mark February 2019	K213998	Calcium scoring and centreline placement in coronary vessels	To assist physicians in performing calcium scoring and in semi-automatic placement of the centreline in coronary vessels	82,106
	Syngo.CT CaScoring (SOMARIS/8 VB50)	Siemens Medical Solutions USA	FDA 510(k) May 2020; CE mark May 2019	K201034	Automated coronary calcium scoring on ECG-gated non-contrast CT	To support the physician in evaluating and documenting calcified lesions in coronary arteries	82,107
	iNtuition-Structural Heart Module	TeraRecon	FDA 510(k) July 2019	K191585	Automatic centreline extraction and automated coronary calcium scoring	To assist in the assessment of calcium in the coronary arteries for calcium scoring	108
	AI-Rad Companion (Cardiovascular)	Siemens Medical Solutions USA	FDA 510(k) September 2019; CE mark August 2019	K183268	Deep learning-based automated coronary calcium scoring on non-gated CT	To support radiologists in the quantification of total calcium volume in the coronary arteries	82,109
	AVIEW	Coreline Soft	FDA 510(k) September 2020	K200714	Automatic deep learning-based calcium scoring; segments and provides overlay of four main arteries and myocardium	To support the segmentation of coronary arteries and quantification of coronary artery calcium scores	110,111
	Cleerly Labs v2.0	Cleerly	FDA 510(k) October 2020	K202280	Deep learning tool to identify high-quality images, segment and label coronary arteries, and segment lumen and vessel walls on CCTA	Not to replace a qualified medical practitioner, but to provide a more robust semi-automatic segmentation software	112,113
	Cardiac Solution (HealthCCSng)	Nanox.AI (Zebra Medical Vision)	FDA 510(k) September 2021	K210085	AI algorithm for coronary calcium scoring from non-cardiac gated, non-contrast CT	Not intended to be used alone, but intended to provide radiologists with an estimated coronary artery calcium detection category (low, medium or high)	114,115
	HeartFlow Analysis	HeartFlow	FDA 510(k) October 2022	K213857	Automatic machine learning-based detection and characterization of coronary artery plaques	Intended to support risk assessment for coronary artery disease	116,117
	Autoplaque	Cedars–Sinai Medical Center	FDA 510(k) May 2023	K212758	Automatic deep learning-based vessel, plaque and lumen segmentation	Intended to be used as an interactive tool for viewing and analysing cardiac CT data for determining the presence and extent of coronary plaques	87
OCT	Ultreon 1.0	Abbott	FDA 510(k); CE mark April 2021	K210458	Automatic detection of lumen, stent, external elastic membrane and calcium	The physician might use the acquired parameters along with other information to determine if therapeutic intervention is indicated	118,119

AI, artificial intelligence; CCTA, coronary CT angiography; ECG, electrocardiogram.

However, the underlying technologies in a commercial product might not be accessible to the user, leading to the discordance about their availability in clinical practice. Furthermore, most applications have not overcome the technical and regulatory challenges of full automation, and require human intervention[79,80].

To identify relevant research tools and the CE-certified and FDA-certified products for coronary plaque assessment, we analysed AI-enabled and machine learning-enabled medical device databases[81–86] (Table 2). Automated calcium scoring analysis in electrocardiogram (ECG)-synchronized or non-ECG-synchronized CT has been established in numerous cardiovascular imaging software products. Several products focus on plaque assessment in CCTA and numerous research tools that have been evaluated in clinical studies[44,87] are gradually being implemented in clinical practice. Most of the available software packages contain tools for the automatic segmentation of tissue types and anatomical structures, such as the vessel wall and the lumen. However, depending on image quality and the presence of anatomical variants, manual correction, such as centreline correction or vessel wall adjustment and lumen or plaque segmentation, is often still required for quality assurance, calling into question the time savings and cost efficiency of AI-based tools.

Similarly, commercially available CE-certified and FDA-certified products for plaque analysis in intravascular modalities are emerging. The latest OCT software packages incorporate lumen, stent, external elastic membrane and calcium detection, and some even include AI-based plaque assessment[15]. However, AI-based plaque assessment is currently available only for research purposes.

Challenges with AI tools in clinical practice

AI is an emerging technology in cardiovascular imaging, and the future benefits of AI in vulnerable plaque imaging are difficult to predict[80]. Importantly, high expectations should not obscure the challenges that still have to be overcome before AI becomes a standard tool in clinical practice. A major challenge for the development of clinical AI tools is the availability of large, diverse, anonymized and annotated datasets with available outcome data for testing, training and validation. The collection, curation and annotation of large sets of images required for AI development are very time-consuming (Table 1). The quality of the annotations is also an important concern, and the expertise required for annotation will depend on the task in question. In addition, AI tools must be tested on external validation datasets with clinical outcomes to ensure their generalizability to wider populations. Poor image quality can also cause difficulties for AI development and use. Many AI tools are trained on curated and annotated datasets with high image quality and, therefore, under-perform in real-world clinical practice. In addition, image artefacts and variation in image acquisition might preclude the use of AI tools or result in inaccurate or unreliable output (Table 1). Standardization of image acquisition would aid AI development, including consistent naming, conformity in the reconstruction of algorithms and structured reporting.

For clinical use, an AI-based tool must provide results in a way that clinicians will understand and trust. Machine learning models might generate a probability of a result, but this outcome is not usually communicated by the AI tools. Methods to improve interpretability – so-called explainable AI – include dedicated models, post hoc assessments, feature importance and graphical visualization. Code, data and model sharing can also help other researchers to reproduce research results and to facilitate clinical uptake, but might be challenging in terms of data privacy and research use of data. Large-scale prospective RCTs of the clinical utility of cardiovascular imaging AI tools have not been conducted[88]. For the assessment of certain tasks, such as segmentation, such trials might not be required. However, for many tasks that can affect subsequent patient management, it is imperative that AI tools meet the same clinical standards as other medical treatments, and that both efficacy and cost-effectiveness are assessed. A 2022 systematic review found only 41 RCTs of medical AI tools, with none adhering to standardized reporting guidelines, and the overall risk of bias was high in seven of these trials[89]. The selection of appropriate metrics to assess the capabilities of AI tools is essential, as is the use of standardized reporting guidelines for AI research. Given that AI tools must be integrated into the usual clinical workflow, an important research task is to investigate how to facilitate human–AI interactions in clinical practice.

Trustworthy AI

Although there is a huge potential for AI to improve clinical coronary plaque imaging, the lack of trustworthy AI approaches remains a serious concern. According to the EU's ethics guidelines[90], trustworthy AI must be lawful, ethical and robust from both a technical and a social perspective (Box 1). In the context of clinical AI solutions, these tools should support decision-making rather than make autonomous decisions, be robust and safe, and provide transparent and unbiased recommendations. In fulfilling these criteria, AI solutions could maximize the benefit for clinicians and patients alike while minimizing the risk to patients.

During clinical deployment, the robustness and safety of AI solutions should be determined in terms of accuracy, reliability and reproducibility. The trustworthiness of AI solutions depends not only on technical aspects, but also on human factors that affect their performance in real-world settings. This requirement necessitates comprehensive and transparent evaluation of AI solutions in accordance with established reporting guidelines. For example, diagnostic accuracy before clinical deployment should be evaluated using the STARD-AI

Box 1

Requirements for trustworthy AI

The following characteristics are required for an artificial intelligence (AI) tool to be trustworthy when applied to the imaging of vulnerable plaques in coronary arteries.

Robust AI
- Technical and clinical robustness (image noise and artefacts, anatomical abnormalities, and evidence from randomized controlled trials)
- Reliability
- Safety
- Real-time decision-making (guided by optical coherence tomography or intravascular ultrasonography)
- Generalizability (patient population and scanner type)
- Technical developments (photon counting CT and reconstruction algorithm)
- Confidence communication of AI (95% CI, heatmap)

Ethical and fair AI
- Safety (recommendation of interventions, such as percutaneous coronary intervention or coronary artery bypass graft surgery)
- Privacy and security (anonymization of patient data)
- Transparency (accessibility of data to the patient)
- Fairness and inclusivity
- Unbiased AI models (for example, no bias against age, sex or ethnicity)
- Explanation and interpretation of automated diagnosis and prognosis for physicians and patients

Lawful AI
- Certification of devices and software (CE-approved or FDA-approved)
- General data protection regulation
- Medical device regulation

guidelines[91], whereas the DECIDE-AI guidelines[92] contain recommendations for evaluating the diagnostic accuracy of the tool in the early phases of clinical deployment. Finally, the CONSORT-AI guidelines[93] for the evaluation of AI solutions should be used in the context of RCTs. The question of when RCTs are needed to verify clinical effectiveness and to test advantages over standard care and when retrospective studies are sufficient for the evaluation of simple human tasks (such as segmentation tasks) is controversial among experts (Table 1). In the context of clinical deployment, AI solutions should increase the confidence in the recommendations in a suitable manner, ideally in a quantitative fashion, so that clinicians can easily interpret their output (Table 1).

Explainability, interpretability and generalizability

AI explainability and interpretability are often used interchangeably, but differ slightly in meaning. AI explainability refers to inspecting the AI model interior to confirm its output, whereas AI interpretability more formally puts cause and effect into relation, so that the model output can always be linked back to the model input. These standards are included in the EU ethics guidelines for trustworthy AI[92] and in the WHO guidance on ethics and governance of AI for health[94], as part of a move to ensure transparency and fairness in AI development and deployment (Fig. 4). In the context of atherosclerotic plaque imaging, editable contours for segmentation models or visualization of output probability distributions might be used to provide information on decision-making.

AI models for plaque analysis require careful creation and curation of training datasets to ensure their generalizability. Changes in input data quality could have undesired effects on predictions, such as when models are trained on quality-controlled research data and then applied to clinical data acquired across a variety of clinical situations or with a different imaging technique, or when AI software for atherosclerotic plaque analysis trained on datasets acquired with energy-integrated detectors might fail when applied to photon-counting CT datasets. Solutions for dealing with these domain shifts include: transfer learning, in which the model is retrained on a small subset of the new data; data augmentation, by simulating the new domain properties; use of training data from a large variety of domains; and a combination of these techniques[95]. Finally, differences in plaque annotations by different radiologists with varying levels of experience and expertise can also lead to differences in model performance. In these cases, model output uncertainty should be reported to inform a clinician to revisit their own findings, or to include annotation uncertainty in the model training for more robust output. The QCI experts of this Roadmap reached a consensus that multiple observers in training datasets are required to compensate for interobserver variability and provide generalizability and can support the uncertainty estimation process.

Fairness and bias mitigation in plaque imaging

Data-driven AI solutions are susceptible to biases that can amplify health-care disparities[96–98], which is an important area of concern. In the context of imaging of vulnerable plaques in coronary arteries, bias can arise from systematic errors such as disproportionate over-representation or under-representation of certain patient subgroups, over-representation of patients at high risk of disease, or applying AI solutions to subgroups who were not included in the initial training (for example, using an AI model in patients with stable chest

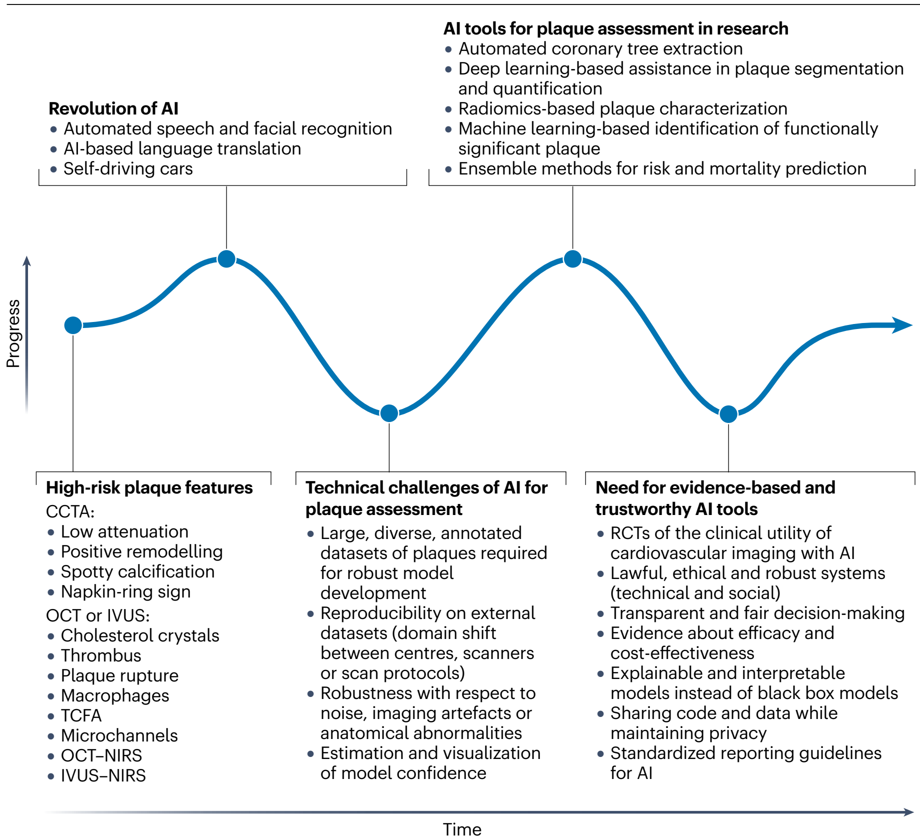

Fig. 4 | Roadmap for AI in the imaging of vulnerable plaques. The figure shows the advances and regressions that have occurred during the integration of artificial intelligence (AI)-based tools into clinical practice, starting from clinical evidence for high-risk plaque features through the revolution of AI, technical challenges for AI for plaque assessment, available AI tools for plaque assessment in research, and the need for evidence-based and trustworthy AI tools. CCTA, coronary CT angiography; IVUS, intravascular ultrasonography; NIRS, near-infrared spectroscopy; OCT, optical coherence tomography; RCT, randomized controlled trials; TCFA, thin-cap fibroatheroma.

pain when it was trained in patients with acute chest pain). Unequal representation in training datasets can particularly affect ethnic and other minority groups, in which AI solutions might perform poorly if these groups were not included in the training datasets[99].

Two main sources of bias exist: first, in the data used to train AI algorithms and, second, in the implementation and deployment of these AI algorithms[100]. Representation biases can be addressed during the collection or preprocessing of training data via reweighting or resampling of minority groups in the training data or via data augmentation[100,101]. Ideally, clinical data used to train AI algorithms should be based on data from large-scale clinical trials with a pragmatic trial design and minimal exclusion criteria to ensure high external validity.

In addition, features used in training can be adjusted not to correlate with sensitive attributes or to use adversarial learning approaches to de-bias AI solutions. When an AI solution has been developed, it is possible to reduce any biases in its performance by using techniques such as calibrated equalized odds (Table 1).

Conclusions

Coronary plaque burden and type are important prognostic markers and can guide patient management. A variety of non-invasive and invasive imaging modalities can be used to assess plaque and identify vulnerable plaques. The revolution and the hype surrounding AI have inspired clinicians and scientists to develop tools to automate the assessment of vulnerable plaques. AI has the potential to transform plaque assessment by improving speed and accuracy, but before fully automated AI tools can be integrated into clinical practice, numerous technical challenges must be addressed (Fig. 4), including reproducibility, robustness, generalizability and reliability, and AI tools must be evaluated using large and diverse datasets. AI tools in research have achieved near-human performance in various plaque assessment tasks, but have mainly been validated in small, preselected and biased study populations. Evidence from RCTs of the clinical utility and cost-effectiveness of approved commercial software solutions is still lacking. Concepts for developing and evaluating trustworthy AI systems that are safe, transparent, fair, interpretable and explainable are still limited and need to be adapted for vulnerable plaque assessment.

This Roadmap for the adoption of AI tools applied to the imaging of vulnerable plaque in coronary arteries includes the development of novel AI tools for the identification of vulnerable plaques in coronary arteries while addressing the many challenges of AI that have been described. Optimizing the integration of AI tools into the clinical workflow will provide coronary plaque metrics together with other clinical and imaging markers of coronary artery disease, including physiology, flow and pericoronary structures. If this Roadmap is adopted, the use of AI systems in close collaboration with physicians[102] to facilitate the imaging of vulnerable plaque in coronary arteries has the potential to revolutionize the diagnosis, prognostic assessment and management of patients with coronary artery disease.

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Author contributions

B.F. and M.D. researched data for the article. B.F., M.C.W. and M.D. contributed to the discussion of content. B.F., M.C.W., D.D., A.A.-Z., P.M.-H., R.H.J.A.V., D.R. J.A.S., D.E.N., M.R.D., G.G., V.F., A.J.V.M., F.B., I.I. and M.D. wrote the manuscript. All authors contributed to reviewing and editing the manuscript before submission.

Competing interests

M.C.W. has given talks for Canon Medical Systems, Novartis and Siemens Healthineers. A.A.-Z. has received research support from Canon Medical Systems. P.M.-H. is a shareholder of Neumann Medical. D.R. has received consultancy fees from Heartflow and IXICO. D.E.N. receives grants, acts as a consultant and has clinical trial contracts with Abbott, Amgen, AstraZeneca, Autoplaque, BMS, Boehringer Ingelheim, Eli Lilly, GE HealthCare, GSK, Janssen, Life Molecular Imaging, MSD, Novartis, Pfizer, Philips, Roche, Sanofi, Siemens, Silence, SOFIE, Toshiba, UCB, Vifor, Wyeth and Zealand. He collaborates with the publications chair from the BMJ Group and Elsevier. He is the chief investigator of the SCOT-HEART and PRE18FFIR trials. M.R.D. has received speaker fees from Edwards, Novartis and Pfizer and consultancy fees from Beren, Jupiter Bioventures, Novartis and Silence Therapeutics. G.G. has a consultant agreement with Abbott Vascular, Gentuity, Infraredx and Panovision, and has received a research grant in the past 36 months from Abbott Vascular, Amgen and Infraredx. V.F. has received educational grants, fees for lectures and speeches, fees for professional consultation, as well as research and study funds from Abbott, Abiomed, Berlin Heart, Biotronik, Boston Scientific, Edwards Lifesciences, JOTEC/CryoLife, LivaNova, Medtronic, Novartis and Zurich Heart. I.I. has received institutional research grants by Esaote and Pie Medical Imaging and received an institutional research grant funded by Dutch Technology Foundation with the participation of Pie Medical Imaging and Philips Healthcare. She is also a co-inventor on several patents (US 10,176,575 B2; US 10,395,366 B2; US 11,004,198 B2; US 10,699,407 B2) and patent applications (17317746, 16911323) on the detection of functionally significant coronary stenosis. M.D. is the publications chair of the European Society of Radiology (ESR; 2022–2025); the opinions expressed in this article are the author's own and do not represent the view of the ESR. He is also the editor of *Cardiac CT* (published by Springer Nature) and has institutional master research agreements with Canon, General Electric, Philips and Siemens, the arrangements of which are managed by Charité – Universitätsmedizin Berlin. He also holds a joint approved patent on dynamic perfusion analysis using fractal analysis (EPO 2022 EP3350773A1 and USPTO 2021 10,991,109). The other authors declare no competing interests.

Additional information

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