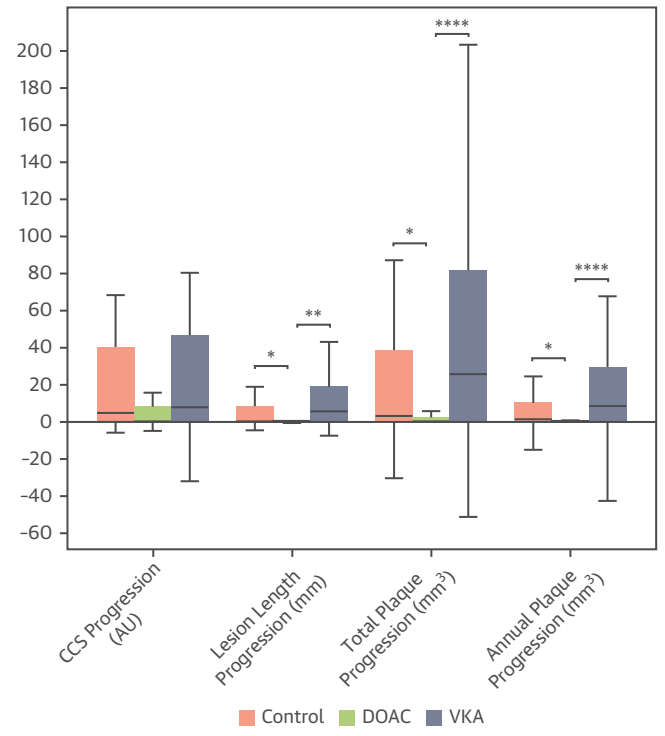
FIGURE 1 CT Results



Boxplot showing changes between baseline and follow-up CT. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. AU = Agatston units; CCS = coronary calcium score; CT = computed tomography; DOAC = direct oral anticoagulation; VKA = vitamin K antagonist.

progressed by 11.1 ± 22.4% for VKA compared with 6.2 ± 24.2% in control and remained stable 0.0 ± 15.4% for DOAC (p = 0.045). CCS showed a similar trend, but did not reach statistical significance (median: 4.8 mm^3 DOAC vs. 0 mm^3 controls vs. 8.6 mm^3 VKA, p = 0.17).

The negative vascular effects of vitamin K inhibition have been substantiated for in vitro and in vivo. In a prospective pilot study, Namba et al. (2) switched 21 patients from warfarin to rivaroxaban, resulting in a significant decrease of atherosclerosis and arterial stiffness.

In contrast, anticoagulation has been shown beneficial in atheroprogression (3). Animal and immunohistological studies highlight the cellular processes affected by protease activated receptors, particularly thrombin (4). Beside its central role in coagulation, it has been linked to inflammatory and atherosclerotic processes. In particular, early-stage plaques were reported more procoagulant compared with advanced-staged atheromas (3).

The difference between patients administered DOAC and VKA in our study is in line with clinical reports, such as the randomized controlled COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, in which addition of low-dose anti-Xa resulted in a reduction of cardiac and all-cause mortality (1). This is also supported by a report from Danish health care registers including 31,739 patients (5).

In summary, in vitro data and clinical trials support the findings of our study that DOAC might reduce or inhibit progression of CAD. Nevertheless, not every plaque translates into clinical significance, and larger cohorts will be needed to elaborate the effect of direct anticoagulation on atherosclerosis.

Christoph Beyer
Matthias Wildauer, MD
Gudrun Feuchtner, MD
Guy Friedrich, MD
Florian Hintringer, MD
Markus Stühlinger, MD
Fabian Plank, MD, PhD*
*Department of Cardiology
Innsbruck Medical University
Anichstr. 35
A-6020 Innsbruck
Austria
E-mail: fabian.plank@i-med.ac.at

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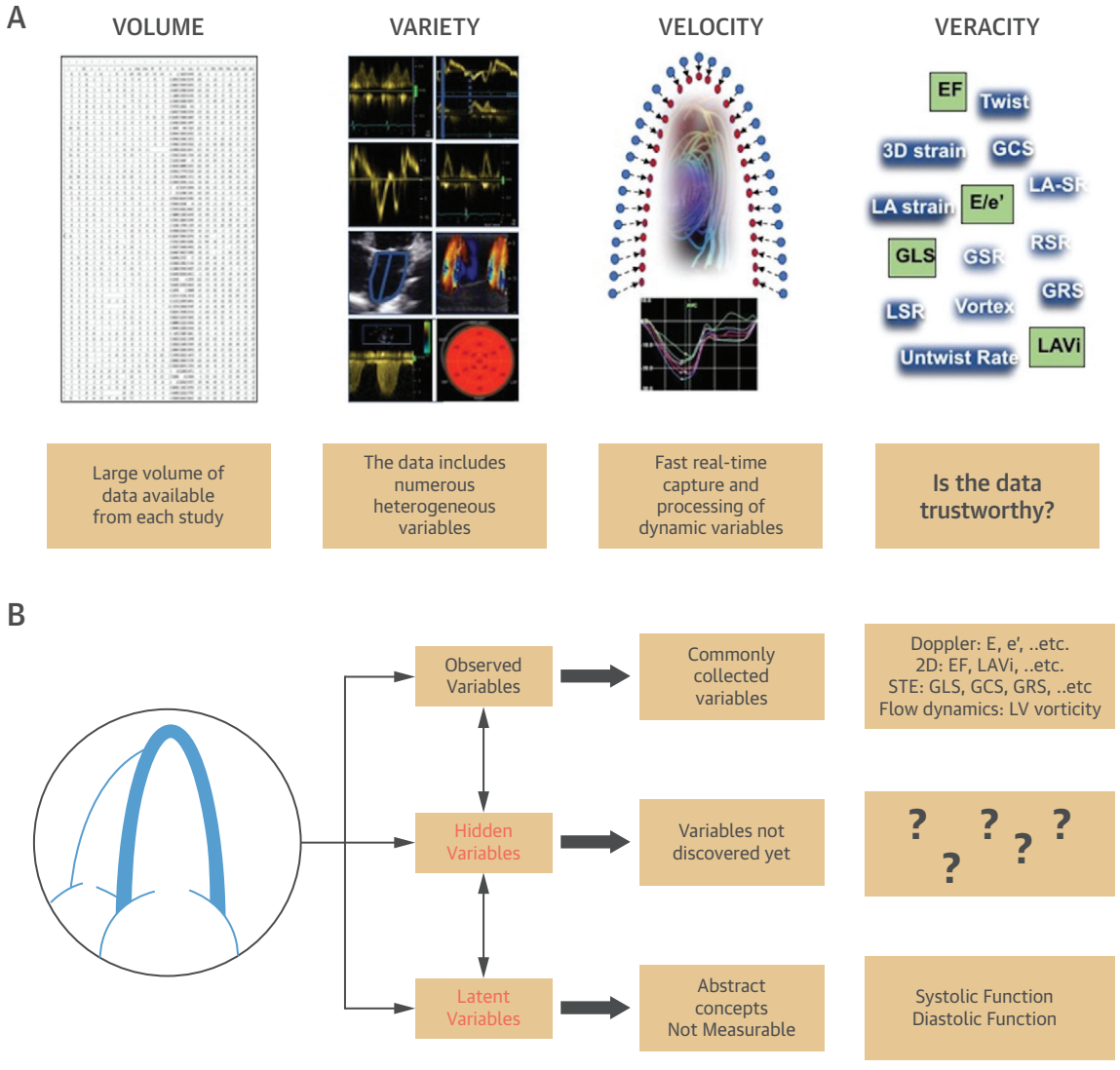
Echocardiographic Data in Artificial Intelligence Research

Primer on Concepts of Big Data and Latent States

Analyses of medical data have been steered to support and justify orthodox systems and graphical models that reproduce the relatively subjective reasoning of experts. Evidence-based decision tree

FIGURE 1 **Concepts of Big Data and Latent Variables as They Apply to Echocardiographic Data**



(A) Big data are characterized by 4 Vs (volume, variety, velocity, and veracity), all of which exist in echocardiographic data. **(B)** An example of interactions among observed, hidden, and latent echocardiographic variables as it applies to diagnosis of myocardial dysfunction. 3D = 3-dimensional; EF = ejection fraction; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; LA = left atrial; LAVi = left atrial volume index; LSR = longitudinal strain rate; LV = left ventricular; RSR = radial strain rate; SR =strain rate; STE = speckle tracking echocardiography.

analyses and risk scores are valid tools for clinical decision-making that are widely used in medicine to guide and standardize complex decisions in daily practice. However, these tools have important limitations largely stemming from their rigidity. They commonly fail to address individual variability and overlook nonlinear relationships between parameters in complex biologic systems (1). Specifically in echocardiography, decision tree analyses rely on rigid categorization of traditional measures of myocardial structure and function, ignoring complex nonlinear interactions and functional overlaps of multiple established and emerging cardiac and noncardiac variables (2). Moreover, many echocardiographic variables have artificial spatiotemporal separation during measurement, subjecting them to time, hemodynamic, and load-related variances. Finally, the plethora of emerging echocardiographic variables can provide unique insights into pathophysiology of myocardial dysfunction. The traditional analytic schemes cannot accommodate the full potential of these data. In contrast, artificial intelligence (AI) has

emerged as a promising tool for operationalizing big data analytics and machine learning (ML) algorithms. Clinicians should be familiar with the basic concepts of ML as they apply to echocardiography.

BIG DATA

Big data are commonly characterized by the 4 Vs (**Figure 1A**): volume (digital amount of data); variety (diversity of sources that make up data); velocity (ability to detect data aspects, analyze them, and reach conclusion in real time); and veracity (differences in reliability among data elements). All of these exist in echocardiographic data (3). Each echocardiographic study consists of several acquisition modes, multiple views, and numerous frames generating large amounts of data. However, echocardiographic data commonly has noise, acquisition and measurement inconsistencies, as well as physiological variability, which raises concerns about potential errors with application of ML-based methods to heterogeneous echocardiographic databases. Rigorous quality assessment and control are essential before implementation of these methods in clinical practice. In contrast, other fields (e.g., genomics) have embraced ML, despite interfacing with noise, and have yielded important outcomes crucial to our understanding of disease processes and drug development. Standards and protocols have evolved to allow for high quality of such analyses (4). Therefore, ML algorithms can be arguably useful for extracting patterns while handling the noise within echocardiographic data.

LATENT AND HIDDEN VARIABLES

Latent variables or states cannot be observed directly but are rather inferred from other, directly measured variables. Certain variables can be "pseudo-latent" or "hidden," meaning they are measurable, but have not been yet discovered. For example, echocardiographic strain variables were hidden until the advent of myocardial deformation imaging using color tissue Doppler (CTDI), which later evolved into speckle tracking echocardiography due to issues with noise and inaccuracies related to CTDI dependence on the insonation angle. It is unknown how many hidden variables exist within echocardiographic datasets, and the future of AI promises discovery of novel measurable variables. However, truly latent variables or states describe abstract concepts inferred from the measurable variables. In echocardiography, diastolic function is an important example of a latent state, which is indirectly inferred from measures of left ventricular relaxation, compliance, and filling pressures. The degree of refinement of the description of diastolic function as a latent state is largely dependent on the number of hidden variables that can be continuously discovered and on the number of data points that can be accommodated by computational modeling (**Figure 1B**).

Methods for latent variable modeling do exist and include factor analysis, principal component analysis, and K-means clustering, among others.

In conclusion, echocardiographic data are suitable for ML algorithm-based research and applications. The appropriate use of AI tools promises reductions in cost, cognitive errors, and variability in clinical settings. These tools can also shed light on the complexity and nonlinear relationships in echocardiographic data beyond rigid traditional analytic approaches.

Alaa Mabrouk Salem Omar, MD, MSc, PhD
Chayakrit Krittanawong, MD
Sukrit Narula, MD
Jagat Narula, MD, PhD
Edgar Argulian, MD, MPH*

*Mount Sinai St. Luke's Hospital
Mount Sinai Heart
Icahn School of Medicine at Mount Sinai
1111 Amsterdam Avenue
New York, New York 10025
E-mail: Edgar.Argulian@mountsinai.org

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Diagnostic Accuracy of a Fast Computational Approach to Derive Fractional Flow Reserve From Coronary CT Angiography

Fractional flow reserve (FFR) is the gold standard to assess the physiological significance of coronary stenoses. Quantitative flow ratio (QFR) is a novel algorithm to compute FFR from imaging data (1). Good diagnostic concordance between QFR and FFR was