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EDITORIAL COMMENT

The Whole Is Greater Than the Sum of its Parts

Combining CT Angiography and Highly Sensitive Troponin in the Diagnostic Work-Up of Patients With Acute Chest Pain*

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First coined by the philosopher Aristotle, the phrase "the whole is greater than the sum of its parts" aptly defines the modern concept of synergy in which the combination of different entities results in substantially improved outcomes compared to single-entity–based approaches. By combining 2 diagnostic pathways of imaging and serum biomarkers, the study by Ferencik et al. (1) in this issue of *iJACC* tantalizingly expands on diagnostic synergistic workflows and adds to the existing scientific literature (1).

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In the field of cardiovascular computed tomography (CT) imaging, such thinking has not been pursued extensively. Early research efforts focused on the improvement of the diagnostic accuracy and reduction of site-effects over the different scanner generations (2). It just happened recently, 10 years after the introduction of 64-slice CT, that the clinical effectiveness of applying cardiac computed tomography angiography (CTA) to different clinical settings has become an important research subject.

The ROMICAT II (Rule Out Myocardial Infarction/Ischemia using Computer Assisted Tomography) trial was a randomized diagnostic trial to determine the value of cardiac CTA in the workup of patients with acute chest pain. This trial is a superb example of the efforts used to determine the clinical effectiveness of a matured imaging technology for broader clinical applicability (3). Consistent with a second randomized diagnostic trial (ACRIN [American College of Radiology Imaging Network PA4005]), ROMICAT II demonstrated that a CTA-based workup strategy allows early discharge (4), particularly in women (5), without altering safety (6).

However, the clinical decision making is less obvious on an individual patient basis. The imaging findings used for clinical decisions are usually categorized as no coronary artery disease (CAD), the presence of nonobstructive CAD, or the presence of a significant coronary stenosis (defined as a stenosis exceeding 50% luminal narrowing). Unfortunately, the proportion of subjects at intermediate risk, usually the group with nonobstructive CAD, remains high (~40% to 50%) and is characterized by a 4% to 5% acute coronary syndrome (ACS) rate. Thus, these subjects require subsequent work-up and testing.

There are several approaches to using additional CT information that enable further stratification of the intermediate risk category. These approaches include the assessment of left ventricular function (7), myocardial perfusion (8), advanced plaque analysis (9), or fractional flow reserve simulations based on CT data (10). However, despite their scientific value, these approaches have not been adopted in clinical practice due to their specific acquisition protocols, insensitivity, or labor-intensive nature. Also, there are promising, non–imaging based strategies, such as high-sensitivity (hs) troponin (Tn) assays emerging (11).

In this issue of *iJACC*, Ferencik et al. (1) present an elegant analysis of the ROMICAT II trial to determine the effect of combining traditional CTA findings with advanced plaque analysis and results from hsTn I tests at the time of presentation to the emergency department. This study provides unique insights into

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the potential synergistic use of different diagnostic pathways.

It is an intriguing finding that both diagnostic strategies share a common challenge, as they leave many subjects in the intermediate risk category (43.8% and 86.9% for CT and hsTn, respectively). Thus, a new understanding of how to interpret very low levels of hsTn produced by higher sensitivity assays may be required. Similarly, the highly sensitive CTA finding of atherosclerotic plaque mandates improved appreciation for the role of plaque in the disease process. Both characteristics are evident in Table 5 of the paper, which demonstrates that the specificity and the associated positive predictive value are relatively low (48.2% and 20.7%, respectively).

Although the effect of a combined approach in excluding the presence of ACS is exquisitely shown in the analysis, the effect size is moderate (see Figure 5 in Ferencik et al. [1]). According to the initial hsTn results, only 13% of subjects could avoid a CT examination, and approximately 5.6% were reclassified for immediate discharge (due to values below the level of detection). Additionally, 7.5% of patients were identified for high-risk management (value >99th percentile). Following the advanced CT analysis, there was a relatively small fraction of subjects further reclassified for immediate discharge (absence of high-risk plaque in 27 of 139, 19.4%) because no plaque was detected in the majority of patients (60 of 139). This is also evident from Table 5 (1) showing that the positive predictive value can only be increased to 29.7%. Table 5 (1) shows the positive predictive value can only be increased to 29.7%. The largest impact of excluding ACS in this population is attributed to the absence of plaque on CT (42.5%). Therefore, the effect of the hsTn measurement remains relatively small.

Thus, major advancements are needed to improve the discriminatory power of the initial hsTn measurement, a field of research that is currently emerging impressively. The challenges to hsTn assays include a lack of industry standards that result in varying assay characteristics and hamper comparisons between hospitals and medical systems (see Online Table 1 in Ferencik et al. [1]). The potential of biological variability also makes interpreting hsTn elevations difficult, and new thresholds must be defined for clinical use (12).

The current analysis does not include other clinical markers of risk that are also available for clinical decision-making. In pooling data from the ADAPT (A 2-hr Accelerated Diagnostic Protocol to Assess patients with chest Pain symptoms using contemporary Troponins as the only biomarker) and APACE (Advantageous Predictors of acute Coronary Syndromes Evaluation) trials, electrocardiogram, Thrombolysis In Myocardial Infarction (TIMI) risk score, and serial hsTn data permitted the safe discharge of up to a quarter of patients (13). Thus, it can be assumed that the combination of CTA results with hsTn and other markers of risk will eventually lead to multiparametric diagnostic pathways and improved triage in this challenging target population.

From an imaging perspective, the rapid availability of CTA with feasible and automated workflows will be essential to establishing imaging information in these fast laboratory-driven pathways, presumably with reporting times of approximately 1 h. A detailed analysis requires substantial expertise and a comprehensive and time-consuming assessment of the CTA datasets, which may not be feasible in a busy emergency department environment on a broader basis. Also, even in the specialized setting of a core lab, the interobserver agreement for high-risk plaque detection is inferior to that of traditional CTA findings such as plaque and stenosis (kappa 0.69 vs. 0.77 and 0.80, respectively) (9). To overcome the restraint of "unlimited time for image interpretation" available in a research core lab, either advanced post-processing tools or straightforward image criteria must be established and verified in real-world scenarios.

In conclusion, the role of serum biomarkers for early myocardial damage and coronary atherosclerotic plaque as determined by cardiac CTA is complementary in the management of patients with acute chest pain. Although both approaches leave a large portion of patients in an intermediate risk category that requires further admission and testing, synergistic workflows can significantly improve the management of these subjects. The present study forms an intriguing basis to justify a large-scale randomized trial to prove that "the whole is greater than the sum of its parts."

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REFERENCES

1. Ferencik M, Liu T, Mayrhofer T, et al. hs-Troponin I followed by CT angiography improves acute coronary syndrome risk stratification accuracy and work-up in acute chest pain patients: results from ROMICAT II trial. J Am Coll Cardiol Img 2015;8:1272–81.

2. Rubin GD, Leipsic J, Joseph Schoepf U, Fleischmann D, Napel S. CT angiography after 20 years: a transformation in cardiovascular

disease characterization continues to advance. Radiology 2014;271:633–52.

3. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med 2012;367:299–308.

4. Schlett CL, Hoffmann U, Geisler T, Nikolaou K, Bamberg F. Cardiac computed tomography for the evaluation of the acute chest pain syndrome: state of the art. Radiol Clin North Am 2015;53:297–305.

5. Truong QA, Hayden D, Woodard PK, et al. Sex differences in the effectiveness of early coronary computed tomographic angiography compared with standard emergency department evaluation for acute chest pain: the rule-out myocardial infarction with Computer-Assisted Tomography (ROMICAT)-II Trial. Circulation 2013;127:2494–502.

6. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med 2012;366:1393–403.

7. Seneviratne SK, Truong QA, Bamberg F, et al. Incremental diagnostic value of regional left ventricular function over coronary assessment by cardiac computed tomography for the detection of acute coronary syndrome in patients with acute chest pain: from the ROMICAT trial. Circ Cardiovasc Imaging 2010;3:375–83.

8. Bezerra HG, Loureiro R, Irlbeck T, et al. Incremental value of myocardial perfusion over regional left ventricular function and coronary stenosis by cardiac CT for the detection of acute coronary syndromes in high-risk patients: a subgroup analysis of the ROMICAT trial. J Cardiovasc Comp Tomogr 2011;5:382–91.

9. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. J Am Coll Cardiol 2014;64:684–92.

10. Park HB, Heo R, o Hartaigh B, et al. Atherosclerotic plaque characteristics by CT angiography identify coronary lesions that cause ischemia: a direct comparison to fractional flow reserve. J Am Coll Cardiol Img 2015;8:1–10.

11. Januzzi JL, Jr. What to expect when measuring high-sensitivity troponin: practical advice for clinicians. J Am Coll Cardiol 2015;65:1665–7.

12. Sherwood MW, Kristin Newby L. High-sensitivity troponin assays: evidence, indications, and reasonable use. J Am Heart Assoc 2014;3:e000403.

13. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. J Am Coll Cardiol 2013;62:1242–9.

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