Conference Paper

Biomarker Diagnostics in Acute Cardiac and Noncardiac Dyspnea: Is There a Role for Point-of-Care Testing?

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The use of biomarkers in acute chest pain and dyspnea is well established and point-of-care testing (POCT) is increasingly used in emergency departments and chest pain units for this purpose. However, few data give evidence that POCT has advantages for the patient or the medical process over central laboratory testing. Especially for troponin testing in patients with myocardial infarction, the newest guidelines define prerequisites on diagnostic test quality which most POC assays do not fulfill. Additionally, no data are available showing that POCT has relevant effect on a change of physician's diagnostic and therapeutic thinking compared to laboratory testing. Regarding patient outcomes and societal costs, central laboratory testing seems to be even superior to POCT. The main limit of currently available POC troponin assays is the higher limit of detection and higher imprecision compared to the new high sensitive laboratory assays. However, new upcoming POC technologies may perform comparable to today's laboratory analyzers.

1. Introduction

Biomarkers are regularly used to guide diagnosis in patients with acute chest pain and acute dyspnea. In acute chest pain—with and without dyspnea—the use of troponins to diagnose acute coronary syndrome is well established, and clear guidelines are available [1]. The same is true for the use of D-dimer to exclude acute pulmonary embolism [2]. In other causes of dyspnea, natriuretic peptides can help to distinguish between a cardiac or pulmonary etiology [3]. In case of infections of the respiratory tract, C-reactive protein is a valuable laboratory marker and blood gas analysis is long-time established for monitoring of ventilation.

Simple test strips or more complex analyzer systems are available for point-of-care testing (POCT) of all of these biomarkers, and many are regularly used in emergency departments, intensive care units, and smaller hospitals as solely available laboratory testing or in ambulatory care.

However, there are few data given evidence if point-of-care testing of cardiac biomarkers has advantages for the patient or the medical process over central laboratory testing.

Diagnostic test quality is defined by six test characteristics which can be used to assess if an assay performs better than another, in our case point-of-care testing versus central laboratory testing. These qualities are (1) technical quality of test information, (2) diagnostic accuracy, (3) change in the referring physician's diagnostic thinking, (4) change in the patient management plan, (5) change in patient outcomes, and (6) societal costs and benefits [4].

2. Technical Quality and Diagnostic Accuracy

With the upcoming of high sensitive troponin assays, demands on technical quality and diagnostic accuracy of troponin are highly increasing [5]. Based on the current ESC/ACCF/AHA/WHF consensus document “Third universal definition of myocardial infarction,” rapid early rule in and rule out of myocardial infarction in acute chest pain patients are possible within 3 hours of admission [1]. Prerequisite is the use of a high-sensitive troponin assay measuring levels as low as about 10 to 60 ng/L depending on the assay

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FIGURE 1: Rapid rule-in and rule-out diagnosis of acute myocardial infarction using high-sensitive troponin T assay. Criteria for rule out: (A) hsTnT <3 ng/L on admission (not part of the guideline!) [10]; (B) no dynamics of hsTnT between admission and 3 h; (C) hsTnT below cutoff value on admission and at 3 h; (D) rise or fall of hsTnT of <20% at 3 h. Criteria for rule in: (E) hsTnT on admission <14 ng/L and rise of >50% at 3 h; (F) hsTnT on admission >14 ng/L and rise or fall of >20% at 3 h; (G) very high hsTnT on admission (level not defined in the guideline, evidence that ~50 ng/L might be a good cutoff value).

used which corresponds to the 99th percentile of a healthy reference population [6]. At this level, a high test quality as reflected by an imprecision of 10% coefficient of variation or less of the respective troponin concentration is required. In clinical populations, the high sensitive troponin T assay is best investigated and used as an example for the assay requirements (see Figure 1) (A) There is new evidence that a troponin T level of below 3 ng/L rules out a myocardial infarction on admission with a sensitivity of 100% (not part of the guideline!) [7]. (B) No dynamics of the troponin value between admission and the 3 h value rules out a myocardial infarction irrespective of the troponin concentration. (C) If troponin levels on admission and at 3 h are below the cutoff value (99th percentile, i.e., 14 ng/L for hsTnT), a myocardial infarction can be ruled out even if there are any dynamics of the troponin values. (D) A rise or fall of troponin T of less than 20% also rules out a myocardial infarction. Criteria for rule in are (E) a level on admission of below 14 ng/L and a rise of >50% at 3 h (F) a troponin T above 14 ng/L on admission and a rise or fall of >20% at 3 h (G) a very high troponin level on admission. This level is not defined in the guideline, but there is evidence that approximately 50 ng/L might be a good cutoff value (specificity of 97%, positive predictive value of 84%) [8].

The required assay performance is only achieved by some of the new(er) central laboratory analyzers and by none of the typical POCT systems [9]. There are also some new small analyzers showing “high-sensitive” measuring qualities which are merchandised as point-of-care systems. However, these systems which show typical technical characteristics of

a central laboratory analyzer but have the ability to measure whole blood are relatively small in size, and ease of use is optimized. Nevertheless, a well-trained person, ideally a medical technician, is needed for operation. Therefore, these systems are rather laboratory analyzers “placed near the patient” than typical point-of-care systems. The typical point-of-care systems are not suited for diagnosis of myocardial infarction based on the current guidelines.

In case of pulmonary embolism, the use of point-of-care D-dimer assays is possible, but only the so-called high-sensitive assays with a sensitivity >95% can exclude pulmonary embolism in patients with low and intermediate probability using the 3-level Wells score. Less sensitive assays, as most of the point-of-care assays are, can only be used in patients “unlikely” for pulmonary embolism using the 2-level Wells score [2]. The use of 2-level instead of 3-level Wells score results in a smaller portion of patients rapidly ruled out by D-dimer testing and more patients to be investigated by ultrasound and CT scanning, respectively.

3. Change in Referring Physician’s Diagnostic Thinking and in Patient Management Plan

Compared to the described clear and unquestionable evidence of troponin and D-dimer guiding the diagnostic process in acute coronary syndrome and pulmonary embolism in patients with acute chest pain, respectively, the effect of biomarkers, including natriuretic peptides, in the work-up of patients with acute dyspnea is less clear. The ESC guidelines recommend two equal alternative diagnostic pathways with echocardiography first or natriuretic peptide testing first [3]. However, there are also studies showing no benefit of biomarker testing in acute dyspnea over the clinical factors diagnostic process [11]. Recommendations for point-of-care testing are not given in the ESC guidelines. The apparently strongest argument for point-of-care testing is the patients benefit by shorter turnaround time giving faster diagnosis compared to central laboratory testing. This topic will be discussed within the next chapter.

4. Change in Patient Outcomes and Societal Costs and Benefits

For troponin testing it could be shown that point-of-care testing is about 50% to 100% less precise in predicting the outcome, all-cause death and cardiovascular death, in acute chest pain patients with elevated troponin levels compared to central laboratory (high-sensitive) troponin testing. Additional, 12% to 28% less patients at risk were identified by the point-of-care assays depending on the point-of-care and central laboratory assay used [12].

In acute dyspnea patients without acute coronary syndrome, slightly elevated high-sensitive troponin T levels indicate a 2.3 times higher risk for all-cause death within 12 months showing another gain in information by using the new high-sensitive assays [13].

A central discussion point is the gain of time by using point-of-care cardiac biomarkers testing in terms of a shorter

turnaround time. Several studies show that using point-of-care testing is shortening the mean time from ordering the blood draw to delivery of the result to the physician by about 40 minutes [14, 15]. However, clinically more important are time scales, as time from symptom to therapy (outcome) or time from arrival to transfer from emergency department. In these time scales the laboratory process is only a smaller portion of the whole process time, and these complex processes are also shortened by use of point-of-care testing but significantly less than the laboratory turnaround time [16]. If there should be a need of shortening the laboratory turnaround time, other measures as optimizing the laboratory workflow by implementing six sigma processes or implementation of total laboratory automation are other proven alternatives to point-of-care testing [17, 18].

From an economical point of view, shortening of the length of stay in emergency room might be cost saving. For troponin testing in emergency department and chest pain unit, several studies investigated the effect of point-of-care testing on the length of stay and most could not find an effect [15]. In one major randomized study, (RATPAC) Randomised Assessment of Treatment using Panel Assay of Cardiac markers trial, more patients were successfully discharged home early within 24 h (32% versus 13%) and the mean (8.8 h versus 12.2 h) but not median length of stay was reduced by use of Point-of-Care testing [19]. On the other hand more patients were managed on cardiac care (4% versus 3%) if point-of-care testing was used [19], and there was no difference in total number of patients admitted to the hospital [20].

From the point of view of patient outcomes, the RATPAC trial showed that point-of-care testing is more expensive (about 21% higher incremental mean costs), which results in a slight, not significant, loss of quality adjusted life years (QALY) for the patient, and the probability that standard care (laboratory testing) is dominant over point-of-care testing was calculated with 89% [19]. The slight loss of QALY and higher costs by using point-of-care testing were attributed to the (partly) unnecessary utilization of cardiac care in this patient group. This is not compensated by the early hospital admissions saved in the point-of-care testing group which are brief in effect and relatively inexpensive [19].

5. Conclusions

The presented assessment of cardiac biomarker testing is summarized in Table 1: (1) currently available point-of-care testing systems have significantly lower technical quality (1) and lower diagnostic accuracy (2) than laboratory testing; this is especially true for troponin testing. There are no data available showing that point-of-care testing has relevant effect on a change of referring physician's diagnostic thinking (3) or a change in the patient management plan (4) compared to laboratory testing, but this is also true for laboratory testing of natriuretic peptides in acute dyspnea as BNP or NTproBNP where data for a positive effect of biomarker testing compared to clinical judgment are sparse. At least for troponin testing, very good data are available that laboratory testing, is superior to point-of-care testing in terms of change

TABLE 1: Comparison of point-of-care testing and central laboratory testing regarding diagnostic test quality (criteria based on [4]).

	POCT	Central Lab
(1) Technical Quality of test information	–/(+)	+
(2) Diagnostic Accuracy	(+)	+
(3) Change in the referring physician's diagnostic thinking	–/+	+
(4) Change in the patient management plan	–/+	+
(5) Change in patient outcomes	(–)	+
(6) Societal costs and benefits	(–)	+

in patient outcomes (5) and regarding societal costs and benefits (6), respectively.

The main reason that point-of-care troponin testing does so relatively poorly is the assay quality in terms of lower limit of detection and imprecision where the new high-sensitive laboratory assays are far ahead today. However, new upcoming point-of-care technologies show very promising performance data, and very likely next generation of point-of-care assays will perform comparable to today's laboratory analyzers [21].

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