Review

Prognostic value of cystatin C in acute coronary syndromes: enhancer of atherosclerosis and promising therapeutic target

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The dynamic balance between cathepsins and CC modulates the catabolism of proteins and different physiological pathways (i.e., neutrophil chemotaxis and tissue remodeling) (1). Cystatin C (CC) is an endogenous inhibitor of cathepsins, which are cysteine proteases secreted by all nucleated cells. Its alteration is shown to cause the onset of various pathological conditions, such as cancer and cardiovascular diseases (CVD) (2, 3). The lack of expression or diminished release of CC is reported to trigger increased cathepsins, resulting in extracellular matrix (ECM) degradation and onset of inflammation (1).

Figure 1 displays the physiopathological mechanisms triggered by the unbalance between CC and cathepsins. These ones are reported to lead to the genesis and the progression of diseases with a known inflammatory hub, such as atherosclerosis (3–10). Several inflammatory cytokines contribute to perturb the CC-cathepsins equilibrium, exerting pleiotropic effect on different cell types, and promoting increased cathepsins levels or on the contrary the release of CC (3). Consequently, increased cathepsin levels promote a wide spectrum of simultaneous cellular activities, such as migration of macrophages, ECM degradation, activation of endothelial cells, lipid accumulation in vascular wall, mainly exacerbating the evolution of atherosclerotic plaque (5–9).

Consequently, increased cathepsin levels promote a wide spectrum of simultaneous cellular activities, such as migration of macrophages, ECM degradation, activation of endothelial cells, lipid accumulation in vascular wall, mainly exacerbating the evolution of atherosclerotic plaque (5–9). A positive feed-back enhances the production of pro-inflammatory cytokines, which can interact with the environment rich in cathepsins. This appears to be critical to trigger thrombotic complications and the further onset of acute cardiovascular events (i.e., myocardial infarction) (3). To support this physiopathological pathway, a severe decrease of CC expression and a consistent increase of cathepsins expression were reported in human atherosclerotic lesions in comparison with normal vessel wall (5, 6, 8). Moreover, high cathepsins levels were shown to enhance the atherosclerotic plaque size and its rapid destabilization, by stimulating ECM degradation and the recruitment of macrophages and T cells at the lesion (6–8).

The cellular secretion of CC levels in the bloodstream is modulated by a complex network of pro-inflammatory cytokines, but the marker increase is mainly induced by transforming growth factor β1 (TGFβ1), which counterbalances the evolution of inflammation by affecting the leukocytes phagocytosis and chemotaxis (2, 11). Taking together all evidences from basic and genetic research, several authors support the hypothesis that high serum CC levels could predict the risk for atherosclerosis, according to the detection of an ongoing lively inflammatory process.

Preliminary findings on healthy subjects showed the prognostic value of CC vs. the occurrence of heart failure, hypertension, diabetes and metabolic syndrome, which represent the conventional risk factors for CVD (12–15). Further studies on patients with or without a history of CVD reported a positive association between higher marker levels and recurrence of adverse cardiovascular events (16–18). The most
Figure 1  Cystatin C, inflammation and atherosclerosis: linking known physiopathological mechanisms.

The unbalance between cystatin C and cathepsins, underlying atherosclerosis and other diseases with a known inflammatory hub (cancer, autoimmune disease, osteoporosis, renal impairment) is reported. On the left, there are reported the inflammatory cytokines mainly contributing to perturb the CC-cathepsins equilibrium, exerting pleiotropic effect on different cell types. Some factors as TGFβ1, vessel endothelium growth factor (VEGF), fibroblast growth factor b (bFGF), tumor necrosis factor α (TNFα), interferon-γ (IFNγ), stimulate macrophages (M), smooth muscle cells (SMC), endothelial cells (EC) to release high levels of different cathepsins (i.e., S, L, K, B, H). On the contrary, TNFβ and bFGF inhibit ECs, whereas TGFβ1 stimulates SMCs to release CC. Increased levels of cathepsins promote a wide spectrum of simultaneous cellular activities, such as migration of Ms, ECM degradation, endothelial activation [expression of vascular cellular adhesion molecule-1 (VCAM1)] and macrophage chemoattractant protein 1 (MCP1)] on the surface of vascular ECs, lipid accumulation in vascular wall, thus exacerbating the evolution of atherosclerotic plaque. A positive feed-back enhances the production of pro-inflammatory cytokines which can interact with the environment rich in cathepsins. This may be critical to trigger thrombotic complications and the further onset of acute cardiovascular events (i.e., myocardial infarction). TGFβ1, transforming growth factor β1; VEGF, vessel endothelium growth factor; bFGF, fibroblast growth factor b; TNFα, tumor necrosis factor α; IFNγ, interferon γ; TGFβ, tumor necrosis factor β; M, macrophages; SMC, smooth muscle cells; EC, endothelial cells; ↑, increase; ↓, decrease; ECM, extracellular matrix; VCAM-1, vascular cellular adhesion molecule-1; MCP1, macrophage chemoattractant protein 1; LDL, low density lipoprotein; T, T cell lymphocytes; FC, fibrosis cap.

A plausible pathological link initially seemed to be renal impairment, since CC can be used to assess kidney dysfunction, at a sub-clinical stage (19). However, the fact that renal impairment is joined to and probably promoted by renal microvascular inflammation (20, 21), further supported the hypothesis that increased serum CC levels might be stimulated by inflammation and worsened by reduced renal clearance.

In this perspective CC might be a systemic sensitive marker of a general ongoing inflammatory process that is the leading pathological mechanism promoting several diseases, such as acute coronary syndromes (ACS) (18). In particular the detection of CC in these patients might improve their risk assessment and also their therapeutic management in a context of secondary care. In fact over the past decade, the elucidation of the catalytic mechanism and fine structural features of CC as an inhibitor of cathepsins, made the design of protease inhibitors feasible and suitable for therapeutic purposes (10). The further pharmacologic development of cystatin-like protease inhibitors has yet shown promising results in treating osteoporosis and osteoarthritis (22). These findings encourage further exploration of CC as a new therapeutic target also in ACS framework, however, a preliminary evidence of marker prognostic value in this specific subset of CVD patients is required.
Aim of the study

We sought to show the prognostic value of CC serum levels in ACS patients, by reviewing available clinical literature. Several reasons could support the interest in this evaluation: 1) the physiopathological involvement of CC expression in the progression of atherosclerosis; 2) clinical evidence on the significant prognostic value of CC levels vs. adverse cardiovascular events in patients with or without a history of CVD; 3) the need to improve the risk assessment in ACS patients, thrusting the search for novel biomarkers to be integrated in the standard risk algorithms; 4) the need for exploration of new therapeutic targets, particularly related to inflammation, in order to enhance the management and the secondary prevention of these patients.

Methods

The Medline Search by Pub Med (from 1966), Embase (from 1993), Ovid (from 1966) till February 2010, with MeSH Terms: “Heart OR Cardiovascular Disease AND Cystatin”, with limits: “Title/Abstract”, was conducted to identify original articles in which serum/plasma CC measurements were investigated as a prognostic marker for fatal and non-fatal cardiovascular events, in patients with ACS. From 277 papers, 15 longitudinal observational studies were preliminary considered (16, 18, 23–35) and a further selection, according to the appropriateness of the statistical methods for survival analysis allowed exclusion of three studies (16, 29, 32). Two studies (29, 32) simply evaluated the association between marker levels and presence of major adverse cardiovascular events (MACE), by comparing the means of CC levels between MACE and not MACE groups, in ACS cohorts according to independent sample t-test. One study (16) excluded participants with a history of myocardial infarction from the analyses of the incidence of events and thus was not useful to the purpose of this work. Finally, 12 papers were selected (18, 23–28, 30, 31, 33–35) according to the following criteria: 1) consistent presence (nearly 50%) of ACS patients when studies were performed on patients with a general coronary heart disease (CHD); 2) Kaplan-Meier method for the estimation of event-free survival during follow-up; 3) log-rank test to compare differences between survival curves according to different CC levels; 4) proportional-hazard model to perform multivariable analyses. Furthermore, the level of evidence was defined according to GRADE classification (36).

Results

The features of the study design and the main results for all considered papers are reported in Table 1. Except for one (25), serum/plasma CC levels were detected with standardized assays for clinical practice by an automatic analyzer, with a net prevalence of nephelometric immunoassay (Dade Behring, Inc., Deerfield, IL, USA) (37). Generally blood samples were collected at Cardiac Care Unit admission (24–26, 28, 30, 31, 34, 35) or at rehabilitation center and in some cases in outpatient setting at study appointment. In most cases, specimens were stored at about –70/-80°C.

Reference population

According to the features of the case series, the studies were classified into four groups. Group A: seven studies on CHD and chest pain (CP) patients including nearly 50%–60% ACS patients (Table 1: 18, 23, 27, 28, 31, 33, 35). Group B: three studies on non ST-elevated ACS (NSTEACS) patients with a variable sample size (24, 30, 34). Group C: one study blending ST elevated myocardial infarction (STEMI) and NSTEACS patients (25). Group D: one study consisting only of STEMI patients (26). Most studies were ancillary sub-studies on biomarkers, from prospective observational clinical studies (23, 24, 27, 31, 34, 35) or from clinical trials (30). All studies had a consecutive enrolment but only for one (34) the sample size was estimated according to an expected incidence of cardiovascular events in the case series. Moreover, restricted selection criteria were not generally adopted, since only three studies excluded patients carrying active infections, neoplastic diseases, renal dysfunction (24, 25, 34) as confounding conditions affecting marker interpretation.

Length of follow-up and outcome

The time to adverse outcome widely varied across different studies despite a similar outcome (Table 1). Six studies considered a variable long-term follow-up ranging from 2.8 to 5.8 years to evaluate the composite incidence of fatal and non-fatal CVD (23, 27, 33), the single incidence of: death or MI (18, 28, 30, 35). Three studies reported 1 year follow-up to evaluate the composite incidence of: death, MI and unstable angina (UA) (24, 25, 34). Four studies considered a short-term follow-up (6 months) to report data on the cumulative incidence of fatal and non-fatal cardiovascular events (26), on the cumulative and single incidence of death and MI (28, 31, 35).

CC prognostic thresholds

In clinical practice, the minimum marker level showing a prognostic value vs. a defined adverse outcome is considered as the prognostic threshold. Across these studies, there is not a general agreement on the definition of such a value, which ranges from 0.93 to 1.3 mg/L. In most studies, patients were partitioned according to the quantiles (quartiles, quintiles or tertiles) of CC levels (18, 23, 24, 27, 28, 30). Thus, in this case, the evaluation of CC threshold level, prognostic for the outcome, emerged from the comparison of the hazard ratios (HRs) between the patients included in the quantiles. Other studies performed a receiving operating characteristic (ROC) curve analysis to determine the optimal CC threshold level to predict cardiovascular events during follow-up (26, 31). The best threshold was identified resorting to the rule of the
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Case series</th>
<th>% ACS patients</th>
<th>Country</th>
<th>Assay</th>
<th>Study type</th>
<th>Sample matrix; storage</th>
<th>Collection</th>
<th>Outcome</th>
<th>Median follow-up</th>
<th>CC threshold</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>(18)</td>
<td>2162</td>
<td>Prevalent ACS</td>
<td>Europe</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Plasma; ~80°C</td>
<td>Cath Lab admission</td>
<td>Cardiac death</td>
<td>3.6 years</td>
<td>0.93 mg/L</td>
<td>1.94 (1.59–2.37)</td>
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<td></td>
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<td>% not available</td>
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<td>AtheroGene Study</td>
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<td>3.6 (2.09–6.14)</td>
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<td>(23)</td>
<td>979 CAD</td>
<td>54% MI</td>
<td>USA</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Serum; ~70°C</td>
<td>S.A.</td>
<td>Composite of: stroke, MI, cardiac death</td>
<td>3.5 years</td>
<td>1.3 mg/L</td>
<td>1.72 (1.10–2.70)</td>
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<td>NSTEACS</td>
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<td>Heart and Soul Study</td>
<td>~80°C</td>
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<td>(24)</td>
<td>525</td>
<td>37% UA; 63% NSTEMI</td>
<td>Europe</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Serum; ~70°C</td>
<td>CCU admission</td>
<td>Composite of: cardiac death, non fatal MI, UA</td>
<td>1 year</td>
<td>0.93 mg/L</td>
<td>1.57 (1.04–2.49)</td>
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<td>SIESTA Study</td>
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<td>(25)</td>
<td>160 ACS</td>
<td>37% STEMI; 30% NSTEMI; 33% UA</td>
<td>Turkey</td>
<td>EI</td>
<td>Observational prospective</td>
<td>Serum; ~70°C</td>
<td>CCU admission</td>
<td>Composite of: cardiac death, non fatal MI, UA</td>
<td>1 year</td>
<td>1.05 mg/L</td>
<td>9.62 (2.3–40.5)</td>
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<td>(26)</td>
<td>71 STEMI</td>
<td>100% STEMI</td>
<td>Japan</td>
<td>CIA</td>
<td>Observational prospective</td>
<td>Serum; storage not available</td>
<td>CCU admission</td>
<td>Composite of: death, non fatal MI, revascularization, stroke, HF</td>
<td>5.6 months</td>
<td>0.96 mg/L</td>
<td>2.17 (1.07–6.98)</td>
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<td>(27)</td>
<td>979 CAD</td>
<td>54% MI</td>
<td>USA</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Serum; ~70°C</td>
<td>S.A.</td>
<td>Death; CVE; HF</td>
<td>3 years</td>
<td>1.3 mg/L</td>
<td>For death: 3.6 (1.8–7.0) For CVE: 2.0 (1.0–3.8) For HF: 2.6 (1.0–6.9)</td>
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<td></td>
<td>Heart and Soul Study</td>
<td>~70°C</td>
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<td>(28)</td>
<td>726 CP</td>
<td>52.3% NSTEACS</td>
<td>Europe</td>
<td>DB</td>
<td>Observational prospective</td>
<td>Plasma; ~70°C</td>
<td>CCU admission</td>
<td>Death; MI</td>
<td>3.3 years for death</td>
<td>1.00 mg/L</td>
<td>For death: 3.2 (1.2–8.5) For MI: n.s.</td>
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<td>(30)</td>
<td>1128</td>
<td>100% NSTEACS</td>
<td>Europe</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Plasma; ~70°C</td>
<td>CCU admission</td>
<td>Death; MI</td>
<td>6 months for MI</td>
<td>1.01 mg/L</td>
<td>For death: 2.04 (1.2–4.1) For MI: 1.95 (1.05–3.63) OR = 5.6 (1.9–16.3)</td>
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<td></td>
<td>NSTEACS</td>
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<td>ICTUS trial</td>
<td>~70°C</td>
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<td>(31)</td>
<td>452 CP</td>
<td>31% MI; 18% UA</td>
<td>Europe</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Plasma; storage not available</td>
<td>CCU admission</td>
<td>Composite of: death, MI</td>
<td>6 months</td>
<td>1.28 mg/L</td>
<td>2.15 (0.93–4.92)</td>
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<td>FAST II and FASTER I studies</td>
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<td>(33)</td>
<td>1033 CHD</td>
<td>58.3% MI</td>
<td>Europe</td>
<td>DB</td>
<td>Observational prospective</td>
<td>Plasma; storage not available</td>
<td>Rehabilitation center CCU admission</td>
<td>Composite of fatal and non fatal CVE</td>
<td>2.8 years</td>
<td>1.24 mg/L</td>
<td>2.27 (1.05–4.91)</td>
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<td>(34)</td>
<td>610</td>
<td>36% UA; 64% NSTEMI</td>
<td>Europe</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Serum; ~80°C</td>
<td>CCU admission</td>
<td>First end point: composite of death, UA, MI, PCI, CABG</td>
<td>1 year</td>
<td>ND</td>
<td>For the first end point: n.s. For second endpoint: 2.15 (0.93–4.92)</td>
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<td>SIESTA</td>
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<tr>
<td>(35)</td>
<td>453 CP</td>
<td>31.3% MI; 18.1% UA</td>
<td>Europe</td>
<td>DB</td>
<td>Sub-study from</td>
<td>Plasma; storage not available</td>
<td>CCU admission</td>
<td>Second end point: composite of death and non fatal MI</td>
<td>6 months</td>
<td>ND</td>
<td>At 6 months: 8.4 (1.0–71.7) At 5.8 years: 6.3 (2.8–14.5)</td>
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*aThe HR is the corresponding risk associated to a change of one unit of CC. *Considering only the group of NSTEACS. *OR since a fixed follow-up time length. Ref., reference number; CC, cystatin C; ACS, acute coronary syndromes; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; DB, Dade Behring Assay, Inc., Deerfield, IL, USA; Cath Lab, catheterization laboratory; MI, myocardial infarction; S.A., study appointment; NSTEACS, non ST-elevated acute coronary syndromes; UA, unstable angina; NSTEMI, non ST-elevated myocardial infarction; SIESTA, systemic inflammation evaluation in non ST-elevation acute coronary syndrome; CCU, cardiac care unit; EI, enzyme immunoassay (Quantikine HS, R&D Systems Inc., MN, USA); STEMI, ST-elevated myocardial infarction; CIA, colorimetric immunoassay (Alfresa Pharma, Osaka, Japan) on automatic analyzer; HF, heart failure; CVE, cardiovascular events; CP, chest pain; ICTUS, invasive vs. conservative treatment of unstable coronary syndromes trial; FAST II, fast assessment of thoracic pain; FASTER I, fast assessment of thoracic pain by nEuRal networks; n.s., not statistically significant; OR, odds ratio; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ND, not detected.
minimum distance between the ROC curve and the upper left corner, representing the best compromise between true positive (patients with recurrence of adverse event and positive to the test) and false-negative tests (patients with recurrence of adverse event and negative to the test). One study (25) performed ROC analysis to assess CC prognostic cut-point level without specifying the applied rule. In contrast to previous approach, some studies partitioned the patients in two groups with and without adverse events. Then the Cox models included CC levels as continuous variable and the resulting hazard ratio (HR), is the corresponding risk associated to a change of one unit of CC (18, 34, 35).

Prognostic role

Most studies used CHD case series, which included a consistent number of ACS patients. A CC level higher than 1.3 mg/L was a risk factor for the occurrence of fatal and non-fatal cardiovascular events (23, 33), for the occurrence of MI and death (31) and for single death (27). Moreover, in a Cox model considering cardiac troponin I (cTnI) levels >0.1 μg/L and abnormal electrocardiographic (ECG) ischemic changes, the addition of CC levels as continuous variable, increased the prognostic value for the composite occurrence of MI and death, significantly shifting the ROC area under curve (AUC) from 0.73 to 0.80 (31). Similarly other studies reported that one unit CC increase was prognostic for death even after adjusting for patient features and cTnI (35) or N-terminal pro B-type natriuretic peptide (NTproBNP) (18). The risk for death further increased when CC was adjusted for GRACE (Global Registry of Acute Coronary Events) risk score. It shifted from a HR of 8.4 (95% confidence interval, CI: 1.0–71.7) to 14.4 (CI: 2.3–89.4) for death at 6 months, and from a HR of 6.3 (CI: 2.8–14.5) to 7.0 (CI: 3.1–15.8) for long-term mortality. Moreover, the c-statistic was applied to compare the ability to classify risk between the clinical model with and without CC levels. It showed the statistically significant incremental prognostic value contributed by the addition of CC to GRACE risk score (35).

Concerning NSTEMI case series, patients with CC levels higher than 0.93 mg/L were reported at risk for overall fatal and non-fatal cardiac events (24) and in particular patients with CC levels higher than 1 mg/L were at risk for death (28, 30). On the contrary, one study (34) showed that CC levels, such as other inflammatory serum markers [high sensitive C-reactive protein (hsCRP)], failed to provide significant independent incremental prognostic information to clinical variables, for the occurrence of fatal and non-fatal cardiovascular events at 1 year follow-up. Contrasting data are also available on the risk for subsequent MI, probably due to the different length of follow-up (28, 30) (Table 1).

Furthermore, in case series with a net prevalence of MIs (25) and particularly in STEMI (26), patients exhibiting CC levels higher than about 1 mg/L were reported at increased risk for the occurrence of MACEs in comparison to patients with lower levels (median HR ranging from 2.17 to 9.43, Table 1).

Discussion

Clinical research has reported that the progression of atherosclerotic plaques represents the critical process triggering thrombotic complications and acute coronary events (38, 39). In addition, a large body of literature has shown the critical role of CC expression in genesis/progression of atherosclerotic plaque formation (5, 6, 8) and the relation between circulating CC levels and inflammatory processes (3, 10). Several inflammatory markers are currently investigated in the setting of ACS since inflammation is widely recognized as the leading pathological mechanism for atherosclerosis. This aiming to improve secondary prevention and therapeutic management (40).

In clinical practice, inflammatory prognostic markers can aid in identifying those patients requiring an immediate anti-inflammatory intervention, and in some cases, as for CC can be directly exploited as a therapeutic target. The characterization of structural features and catalytic mechanism of CC molecule has allowed the clinical introduction of new anti-inflammatory therapeutic regimens, in diseases other than CVD but with a common inflammatory hub (22). Thus, the yet successful clinical introduction of CC-like protease inhibitors and the known role in the pathology of CVD (3–9), in contrast to hsCRP (41), amplify the clinical application of this marker over the evidence of simple prognostic marker.

In this perspective, joining physiopathological research and pharmaceutical advances, CC might represent a reliable chance to improve the management of ACS patients, potentially being a prognostic marker and a therapeutic target at the same time. The present review aims to clarify some issues concerning the prognostic role of CC in ACS patients, and then its debated value as an index of a general inflammatory process, more than of renal impairment (42–44).

A rather low number of clinical studies on CC in ACS emerged from this work, and in most cases, a general agreement on the prognostic value of the marker was reported. It should be noted though that there was only a low to moderate level of evidence and generally a poor quality of study design. Some evidence (25, 26, 28), on selected subsets of patients (NSTEMI or STEMI patients), could be ascribed to level IV or V of GRADE, for the low sample size. Others are of level II, since ancillary investigations on biomarkers, derived from clinical observational studies or trials, recruiting large case series of patients with heterogeneous clinical features. The selection criteria concerning the case series is a critical issue potentially limiting the inference of results. In fact STEMI, NSTEMI and UA are gauged on various pathological mechanisms which can often differ greatly for features, persistence, degree, and presence (i.e., plaque disruption, thrombosis, coronary artery occlusion, myocardial necrosis, inflammatory reaction). The biomarker circulating levels are modulated by these pathological mechanisms, thus the blending of different case series of ACS patients, as in most studies, should provide only a rough assessment of the marker prognostic value.

Furthermore, the studies reviewed had some gaps in the design, as well as a lack of sample size estimation, which
should account for the length of follow-up and the prevalence of the risk factors in the case series. In particular, it is widely accepted that the ratio between the number of adverse events and the number of variables included in the Cox model should not be <10:1 (45, 46). Reasonably, according to this rule and to the reported high variability of HR estimates, some studies may provide unreliable results (25, 26). Moreover, the length of follow-up, across different studies, seems too variable for the same outcome and could yield conflicting results, as in the case of two studies exploring whether CC levels were prognostic for future MI (28, 30). Furthermore, only some studies included marker levels as a continuous variable in the multivariable regression function to fully explore the potential role of CC (18, 23, 25, 28, 34, 35). In fact, this approach can provide utmost relevant information on the variation of the risk for adverse events according to the patient marker level (18, 34, 35).

Generally marker levels were considered in the models as a categorical variable: dichotomized according to non-homogeneous cut-off values (26, 31), or grouped according to the partition of marker levels in quantiles (23, 24, 27, 28, 30, 33). These studies attempted to assess the prognostic CC threshold level (the minimum concentration of CC predictive for a defined adverse event) useful to identify, in daily clinical practice, those ACS patients at increased risk for an adverse outcome. However, the assessment of a threshold level is prone to criticisms when, as in these studies, it derives from the distribution of patient marker levels and it implies the use of clinical outcome data. In fact, the same threshold level is considered for computing p-values both to compare survival curves of patients above and below that threshold level is considered for computing p-values both to compare survival curves of patients above and below that threshold level and to perform regression analyses involving the marker.

Currently, no standardized assay for CC detection is available, and no recommendations for uniform cut-off values exist, mainly complicating the comparability between studies (18, 47). Although the wide variability of prognostic threshold values and HRs, the rather good agreement between results may be due to the use of the same CC assay (37), suitable for clinical use, across most studies (18, 23, 24, 27–34). The use of automatic analyzers for these studies, clearly improved the accuracy and the precision of the marker level estimates and contributed to the reliability of the findings (47).

The question remains as to whether CC can be considered as a primary index of inflammation, or more a marker of renal impairment (46, 47). In fact, CC is reported to be significantly correlated or associated with both markers/estimations of glomerular filtration rate (18, 24, 25, 27, 28, 30, 31) and hsCRP (18, 24, 27, 28, 30). However, a wide variability of results is due to the clinical features and the selection of patients [i.e., with normal/reduced kidney function (18)]. In addition, both the consistent prevalence of patients with renal impairment, in the clinical setting of CVD, and the lack of data on patients with normal kidney function, estimated by the gold standard method (insulin clearance) mainly prevent from this evaluation (42). However, in the framework of ACS, for the complexity of patients, it seems more relevant to state whether CC could add a higher prognostic value than conventional markers of renal impairment and inflammation to the clinical risk scores. A few recent studies have focused on this aspect but the initial results are rather conflicting (34, 35).

In conclusion, despite low to modest evidences, a general agreement on the prognostic value of CC levels in ACS in addition to pharmacological advancements on CC-like protease inhibitors (22) should encourage further research on more homogeneous case series, such as MI patients. In particular, this ACS subset might benefit from the evaluation of CC since about 70% of adverse events cannot be predicted after a myocardial infarction by a common risk score and prevented by the available drug therapy (40, 48, 49).

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