Prognostic Implications of Myocardial Injury around Percutaneous Coronary Interventions

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 11-03-2019
Chapter 9

Summary and conclusions
This thesis addresses the clinical value of systematic measurements of cardiac biomarkers after percutaneous coronary interventions (PCI). The importance of troponin T (TnT), creatine kinase (CK) and its muscle-brain isomer (CK-MB) is evaluated in patients undergoing elective PCI as well as in patients undergoing primary PCI for ST-elevation myocardial infarction (STEMI).

The first chapter starts with an introduction and overview of this thesis. The number of PCIs has increased during the past decades and research on quality control and clinical implications is mandatory. Part I of this thesis is focused on myocardial injury and the measurement of cardiac biomarkers after elective PCI.

In the second chapter, we describe the findings of a prospective study on 713 unselected patients with elective PCI. TnT elevation (21%) occurred more often than CK elevation (9%). After a mean follow-up period of 10.9 months, postprocedural TnT, but not CK, was significantly associated with the primary combined endpoint of adverse cardiac events. In conclusion, increase of TnT after elective PCI has stronger prognostic implications when compared to increase of CK.

We assessed the influence of pre-treatment with clopidogrel on the incidence of minor postprocedural TnT elevations in the third chapter in a prospective, observational study on 656 patients undergoing elective PCI. TnT was elevated in 34% of the 330 patients without pre-treatment, compared to 30% of the 326 pre-treated patients. After multivariable analyses, patients who were pre-treated with clopidogrel had a significantly lower risk of postprocedural TnT elevation (OR 0.69, 95% CI 0.49-0.99). This effect was found in particular in those with older age, previous PCI, angina CCS 4 and multivessel disease. We concluded that, combined with results of other studies, pre-treatment with clopidogrel should be advised in patients waiting for elective PCI.

In the fourth chapter we describe that patients with elective PCI undergoing multivessel PCI, compared to those undergoing single-vessel PCI, more often had TnT elevation after PCI (31.5 vs. 18.3%, p=0.001). Furthermore, there was a higher incidence of cardiac events during a mean follow-up period of 10.9 months, in those undergoing a multivessel PCI. However, when in a multivariate model correction for the presence of multivessel disease itself was made, this association was not significant anymore. We could conclude that multivessel PCI was associated with more TnT release and that there was a trend towards a higher incidence of cardiac events during follow-up.
Summary and conclusions

We present the results of a meta-analysis in the fifth chapter, including 20 studies involving 15,581 patients undergoing elective PCI. Overall, troponin was elevated after PCI in 32.9% of patients. After a mean follow-up period of 16.3 months, mortality was higher in patients with postprocedural troponin elevation compared to those without troponin elevation (4.4 vs. 3.3%, p=0.001). Furthermore, the combined endpoint of mortality or non-fatal myocardial infarction (MI) occurred more often in patients with troponin elevation (8.1 vs. 5.2%, p<0.001). According to this meta-analysis, troponin elevation after elective PCI provides important prognostic information.

Part II of this thesis is focused on myocardial injury and the measurement of cardiac biomarkers in patients treated with primary PCI.

A study investigating the value of TnT on admission in 444 patients undergoing primary PCI for STEMI is described in the sixth chapter. Elevation of TnT on admission was present in 47% of patients. Presentation delay, anterior MI location and higher age were independent predictors of elevated cTnT on admission. Furthermore, patients with TnT elevation on admission were less likely to have successful primary PCI compared to those without TnT elevation on admission and had significantly higher rates of one-year mortality.

The results of a study on the prognostic importance of CK and CK-MB in 4,670 patients undergoing primary PCI for STEMI are presented in the seventh chapter. Both increased CK and CK-MB were associated with a lower left ventricular ejection fraction (LVEF). One-year mortality was 5.4% and both peak CK and CK-MB were higher in those who died. Patients in the highest tertile of either peak CK or CK-MB had, also after multivariable analyses, a higher one-year mortality, whereas the differences between the two lower tertiles were not significant. We concluded that, in patients undergoing primary PCI, peak CK and CK-MB are independent predictors of LVEF and mortality.

In the eighth chapter, we assess the comparative predictive value of infarct location, infarct size and ejection fraction after primary PCI for STEMI. Low LVEF was a stronger predictor of one-year mortality (OR 4.4) compared to enzymatic infarct size (OR 2.0) or anterior location (OR 1.6). In addition, even after correction for enzymatic infarct size in multivariable analyses, patients with anterior infarction still had an increased risk of a poor LVEF and also a higher one-year mortality. In conclusion, although not as strong as LVEF, infarct location remains an important independent predictor of prognosis in patients after primary PCI.
Final comments

Many patients with coronary artery disease are nowadays treated with PCI and it is the most frequently performed revascularisation therapy [1]. The number of PCIs is still rising over the last years, and a further growth may be expected [2]. The recently published COURAGE trial showed no difference in the occurrence of major cardiovascular events in follow-up between an initial interventional approach compared to an initial conservative strategy in patients with stable angina pectoris [3]. However, this seems to be a very low-risk population, as most patients had minimal or no angina, a well preserved LVEF, and patients with a markedly positive stress test were excluded. Also, an improvement in angina-free status and a reduction in the requirement for subsequent revascularisation was observed in the patients in the interventional arm in that study [4]. As improving quality of life, and not improving survival, was already the main reason for performing PCI in patients with stable angina, this trial will probably not have many influence on the number of PCIs in these patients. Moreover, since invasive treatment has been shown to improve prognosis in patients with ST-elevation acute coronary syndromes (ACS) [5] as well as non-ST-elevation ACS [6], and the fact that there still seems to exist a risk-averse instead of a risk-driven strategy in daily practise in patients with ACS [7], the expected further rise in the total number of PCI, in particular performed for acute coronary syndromes, seems plausible.

Elective PCI

Since the primary goal of elective PCI is to improve quality of life, particularly by reducing anginal complaints, it is important to reduce complications and side-effects to a minimum. STEMI occurs rarely in patients undergoing elective PCI, with reported rates of less than 0.5% [8], but is a serious complication, and the development of new Q-waves has been associated with a worse prognosis [9]. Non-STEMI after elective PCI is more common and is also related to cardiac events during follow-up. This has been shown for minor myocardial injury, as measured by elevations of CK(-MB) and especially troponin according to our analyses.

The measurement of postprocedural biomarker release, especially elevation of troponin, seems therefore suitable to monitor PCI success when applying new techniques and medications. Reduced postprocedural biomarker release has
Summary and conclusions

been shown after treatment with glycoprotein IIb/IIIa inhibitors [10,11], clopidogrel [12], statins [13] or adenosine [14]. Whether patients with postprocedural biomarker release might benefit of more aggressive medical therapy (e.g. increasing or adding beta-blockers, ACE-inhibitors and/or lipid-lowering drugs) or a lower threshold for re-angiography, has to be investigated.

**Primary PCI**

Apart from the ECG at admission, cardiac enzymes and especially troponin at admission are helpful to identify patients with a worse prognosis in those undergoing primary PCI for STEMI [15,this thesis]. This can be in part explained by a longer delay in these patients, and early diagnosis and reperfusion therapy are very important. Efforts to improve prognosis of patients with increased TnT at admission should be made, and the use of glycoprotein IIb/IIIa inhibitors for instance has been associated with improved myocardial perfusion in patients with elevated troponin levels at admission and TIMI-3 flow post-PCI [16].

According to this thesis, peak values of CK and CK-MB predict prognosis in patients treated with primary PCI. Therefore, these enzymes may stratify patients for additional therapies. For example, cardiac enzymes might be superior, possibly next to LVEF, infarct location and other variables, in selecting patients with potential benefit of implantable defibrillators, whereas a low LVEF is nowadays practically the only used criterion [17].

The cardiac troponins are potentially superior again, when compared to CK(-MB), in estimating infarct size and especially predicting prognosis in patients undergoing primary PCI. However, limited studies have been performed on this issue, focusing on late, single values of troponin [18,19]. Therefore, further research is warranted, with attention to the peak values of troponin.

**Other biomarkers**

Brain natriuretic peptides (BNP and/or NT-pro-BNP) are helpful for the detection of congestive heart failure [20]. Although elevations of BNP are prognostic for death in patients with ACS, and women presenting with normal troponin but elevated BNP values may benefit from early PCI [21], the preferred strategy in the individual patient with ACS remains unclear [22]. The admission value of BNP has been reported to be an independent predictor of short-term death and angiographic success after PCI in patients with STEMI [23]. Furthermore, pre-
procedural BNP in patients undergoing PCI for stable angina or non-ST-elevation ACS provides independent prognostic information during follow-up [24]. Moreover, postprocedural BNP has recently been associated with postprocedural CK-MB as well as with TnT levels, probably as a result of hemodynamic stress [25]. Whether a rise of BNP after elective PCI is also associated with prognosis has yet to be investigated.

C-reactive protein (CRP) levels have been associated with the extend of inflammatory state of atherosclerosis in patients with coronary artery disease. In patients with stable coronary disease or acute coronary syndromes, CRP measurement may be useful as an independent marker for assessing likelihood of recurrent events [26]. CRP has been related to infarct size and mortality after primary PCI for STEMI [18]. However, after multivariable analysis only troponin level and Killip-class were independent predictors of mortality in that study. Increase of CRP level after elective PCI may also have prognostic value [27,28].

Heart-type fatty acid binding protein (H-FABP) is a promising biomarker that is released rapidly from the cardiomyocyte in response to myocardial injury. It has comparable kinetics and release as myoglobin, but is more cardiospecific [29]. Recently, H-FABP was shown to provide significant incremental information for risk stratification in patients with ACS, independent of troponin, BNP and myoglobin [30]. H-FABP can be used as a marker of reperfusion success in STEMI patients treated with thrombolytics [31], as well as in patients undergoing primary PCI [32]. There are no data on the prognostic value of H-FABP after elective PCI. Possibly, it can be useful in patients who are planned to be discharged early, although it has been suggested that this can be safe using only patient symptoms, angiographic results and ECG, without biomarkers as selection criteria [33]. Future studies should demonstrate potential benefits of this biomarker.
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