The current practice for cocaine-associated chest pain in the Netherlands

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Introduction: Cocaine is considered a cardiovascular risk factor, yet it is not included in the frequently used risk stratification scores. Moreover, many guidelines provide limited advice on how to diagnose and treat cocaine-associated chest pain (CACP). This study aimed to determine the current practice for CACP patients in emergency departments and coronary care units throughout the Netherlands.

Methods: An anonymous online questionnaire-based survey was conducted among Dutch emergency physicians and cardiologists between July 2015 and February 2016. The questionnaire was based on the American Heart Association CACP treatment algorithm.

Results: A total of 214 subjects were enrolled and completed the questionnaire. All responders considered cocaine use a risk factor for developing acute coronary syndrome (ACS), nevertheless 74.4 % of emergency physicians and 81.1 % of cardiologists do not always question chest pain patients about drug use. Of all responders, 73.6 % never perform toxicology screening. Most responders (60 %) observe patients with Cocaine according to the European Society of Cardiology ACS guideline, and 24.3 % give these patients β-blockers.

Conclusion: The current practice for CACP patients in most emergency departments and coronary care units in the Netherlands is not in line with the AHA scientific statement. Emergency physicians and cardiologists should be advised to routinely question all chest pain patients on drug history and be aware that the risk stratifications scores are not validated for CACP. Despite the AHA scientific statement of 2008, many respondents utilize β-blockers for CACP patients, which is supported by published evidence since the statement appeared.
The aim of this study was to determine the current practice for CACP patients in the Netherlands and if the recommendations are still relevant based on evidence published since 2008.

2. Methods

The study consisted of an anonymous questionnaire-based survey conducted among Dutch emergency physicians and cardiologists and their residents. The survey was conducted over an eight-month period (July 2015 to February 2016), and consisted of eight questions on knowledge of CIMI risk, risk-stratification methods, and clinical management and follow-up for CACP patients. When specialty was missing, subjects were excluded. After feedback on a pilot survey (N = 10) was incorporated, the questionnaire was presented on an online portal (www.surveymonkey.nl; company: Survey Monkey Inc.) and

Table 1: Questionnaire questions and results.

| Domain                  | Question                                                                 | N   | Answers               | Total                         | EP (n = 117, 55.2 %) | Cardiologists (n = 95, 44.8 %) | p-value |
|-------------------------|--------------------------------------------------------------------------|-----|-----------------------|-------------------------------|----------------------|--------------------------------|---------|
| Knowledge of risk       | Within which time frame after cocaine intake would chest pain development lead you to regard cocaine intake as a risk factor for ACS? | 211 | No risk: 0 (0%)       | 0 (0%)                        | 0 (0%)              | 0 (0%)                        | 0.6492  |
|                         | 3 h: 8 (3.8%)                |     | 5 (4.3%)              | 3 (3.1%)                      | 14 (14.7%)          | 0.8879                         |         |
|                         | 6 h: 32 (15.2%)              |     | 18 (15.4%)            | 4 (3.1%)                      | 14 (14.7%)          | 0.8879                         |         |
|                         | 12 h: 27 (12.8%)             |     | 21 (19.9%)            | 6 (6.3%)                      | 0.0119              |                                |         |
|                         | 1 day: 65 (30.8%)            |     | 36 (30.8%)            | 29 (30.5%)                    | 0.9626              |                                |         |
|                         | 4 days: 26 (12.3%)           |     | 11 (9.4%)             | 15 (15.8%)                    | 0.0590              |                                |         |
|                         | >4 days: 48 (22.6%)          |     | 30 (25.6%)            | 18 (18.9%)                    | 0.3222              |                                |         |
| Risk stratification     | Do you take a drug history in a chest pain patient?                      | 212 | Yes, depends on age: 142 (67 %) | 77 (65.8 %)            | 65 (68.4 %)          | 0.7694                         |         |
|                         | Yes, depends on history: 14 (6.6 %)                                     |     | 5 (4.3 %)             | 9 (9.5 %)                     | 0.1311              |                                |         |
|                         | No: 156 (73.6 %)             |     | 130 (88 %)            | 53 (55.8 %)                   | <0.0001             |                                |         |
|                         | Yes, always: 48 (22.6 %)     |     | 30 (25.6 %)            | 18 (18.9 %)                    | 0.3222              |                                |         |
|                         | Yes, depends on age: 52 (24.5 %)                                       |     | 14 (12 %)             | 38 (40 %)                     | <0.0001             |                                |         |
|                         | Yes, depends on history: 4 (1.9 %)                                      |     | 0 (0%)                | 4 (4.2 %)                      | 0.0256              |                                |         |
|                         | No: 28 (13.3 %)              |     | 25 (21.4 %)            | 3 (3.2 %)                      | 0.0001              |                                |         |
| For how long do you observe low risk CACP patients? | Do you perform a toxicology test in a chest pain patient? | 212 | No: 14 (14.7 %)        | 14 (14.7 %)                   | 14 (14.7 %)          | 0.5568                         |         |
|                         | Yes, GRACE: 96 (45.7 %)      |     | 23 (19.7 %)            | 73 (76.8 %)                    | <0.0001             |                                |         |
|                         | Yes, TIMI: 52 (24.5 %)       |     | 2 (1.7 %)              | 3 (3.2 %)                      | 0.4785              |                                |         |
|                         | Yes, HEART: 81 (38.6 %)      |     | 66 (56.4 %)            | 15 (15.8 %)                    | <0.0001             |                                |         |
|                         | Until pain free: 61 (28.8 %) |     | 26 (22.2 %)            | 35 (36.8 %)                    | 0.0198              |                                |         |
|                         | According to the ESC guideline: 127 (60 %) |     | 78 (66.6 %)          | 49 (51.6 %)                    | 0.0271              |                                |         |
|                         | Admission (>24 h): 9 (4.2 %) |     | 7 (6 %)                | 2 (2.1 %)                      | 0.1627              |                                |         |
| Clinical management     | Do you treat CACP patients according to the ESC guideline?              | 206 | No: 14 (14.7 %)        | 14 (14.7 %)                   | 14 (14.7 %)          | 0.5568                         |         |
|                         | Yes, with Î²-blockers: 24 (11.7 %)                                     |     | 20 (17.1 %)            | 4 (4.2 %)                      | 0.0038              |                                |         |
|                         | Yes, with Î²-blockers in the acute phase: 12 (5.8 %)                  |     | 6 (5.1 %)              | 6 (6.3 %)                      | 0.7111              |                                |         |
|                         | Yes, with Î²-blockers only in long term treatment: 99 (48.1 %)        |     | 55 (47 %)              | 44 (46.3 %)                    | 0.9204              |                                |         |
|                         | No: 57 (27.7 %)              |     | 30 (25.6 %)            | 27 (28.4 %)                    | 0.6529              |                                |         |
| Follow-up               | Do you perform invasive diagnostic tests in cocaine associated NSTEMI patients? | 206 | Yes, coronary angiography: 79 (38.1 %) | 79 (38.1 %)            | 79 (38.1 %)          | 1.0000                         | 0.0000  |
| Demographic data        | What is your level?                                                      | 212 | Specialist: 156 (73.6 %) | 95 (81.2 %)            | 61 (64.2 %)          | 0.0035                         |         |
|                         | Resident in specialty training: 56 (26.4 %)                             |     | 22 (18.8 %)            | 34 (35.7 %)                    | 0.0056              |                                |         |
distributed via a web link. Physicians were approached via twitter, the website and newsletter of their national scientific society, flyers and email via their local department secretary. Reminders were sent if appropriate. Geographical data and occupation were collected, and data was maintained and analysed in SPSS (version 12). All data were descriptive. Correlations between the profiles of responders and their responses were determined by means of cross tabulation. A p-value \( p < 0.05 \) was considered statistically significant.

3. Results

A total of 212 subjects were enrolled out of 1740 Dutch physicians (emergency physicians (345), cardiologist (1045) and their residents in specialty training (350)) and completed the questionnaire. Subjects were equally distributed throughout the Netherlands and 55 % were emergency physicians (residents) and 45 % were cardiologist (residents). Most responders (89 %) were employed at teaching hospitals. Results are shown in Table 1.

4. Discussion

This study aimed to evaluate the current practice for CACP in the Netherlands. Although all subjects considered cocaine a risk factor for developing ACS, 77.4 % did not routinely question or test (73.6 %) their patients for recreational drug use. This suggests that physicians underestimate cocaine use in their population.

The self-reported rate for cocaine use in ED chest pain patients varies from 50 to 82% [11–17] with a self-reported sensitivity of 50–77% [12–14]. In 2015, Dutch cocaine samples contained on average 64 % pure cocaine, which was 68 % in 2017 [19]. The cocaine was in 41 % of the samples contaminated with the adulterant levamisole [20]. Therefore, in addition to routinely questioning a chest pain patient for RD use, it is advised to also consider toxicology screening in, especially young, chest pain patients [2].

The GRACE score for risk stratification is frequently used by cardiologists, in accordance with the ESC ACS guideline. [4] Emergency physicians prefer the HEART score. Nevertheless, neither of these scores has been validated for CACP patients. The TIMI score is not valid for CACP patients [20] and a recent study on the HEART score showed that 14 % of CACP patients with a low-risk score experienced major adverse cardiac events compared to 4% of patients without cocaine use [21]. This highlights the necessity of careful interpretation of risk stratification scores.

The majority of subjects (60 %) observed patients with CACP for 3–6 hours, according to the ESC ACS guideline [4,5], regardless of the AHA scientific statement that recommended twelve-hour observation period. [2,6] The 2020 ESC NSTEMI guideline advises a minimal observation of only 2 h in low risk patients with conclusive high-sensitivity cardiac troponin [4]. Whether such ultrashort observational periods can be applied to CACP patients is subject to current research (Netherlands trial register ID NL5243).

The time gap between the use of cocaine and the onset of chest pain symptoms can vary widely, as long as 4 days. [6,22–24] Because of this variety, and cocaine metabolite presence in the circulation up to 48 h after cocaine use, it is difficult to predict optimal observation time to exclude ACS. The AHA scientific statement advises an observation time of 9–12 hours [6,25–27]. It is not clear whether observation time by Dutch physicians is shorter due to a lack of knowledge of the AHA scientific statement recommendations or because these recommendations are generally considered to be outdated.

Little is known about the best diagnostic tests for CMI patients, although most cardiologists (83 %) perform a coronary angiogram (CAG). One study reported platelet-rich arterial thrombi in coronary and cerebral vessels in up to 14 % of cocaine related deaths. [22] Another study showed that 77 % of CMI patients had a significant coronary stenosis, which was 62 % in the study by Agrawal et al., who also concluded that coronary CT results were comparable to CAG [9]. Nevertheless, the AHA scientific statement emphasizes the low risk of clinically significant coronary artery disease, with a low cost-effectiveness and number needed to treat of 59 [10].

The treatment of all ACS patients consists of aspirin and nitroglycerine. [2–6] The treatment for CACP differs slightly, as intravenous benzodiazepines are advised in order to reduce sympathomimetic effects, and AHA guidelines strongly advise against the use of \( \beta \)-blockers for acute cocaine intoxicated patients due to a theoretical unopposed \( \alpha \)-stimulation effect [2,6,10]. They also recommend to avoid \( \beta \)-blockers at discharge because of the high 1-year recurrence rate of cocaine use in CMI patients [28]. Despite this recommendation, almost 25 % of subjects treat patients with \( \beta \)-blockers at some point. Like our study, Gupta et al. found that the majority of CACP patients, although significantly less often (85.8 % vs 90.1 %, \( p < 0.0001 \)), were treated with \( \beta \)-blockers, compared to cocaine negative patients. [29]. This may be because the ESC guidelines [4,5] do not give any advice on CACP, or because physicians consider the AHA advice outdated and \( \beta \)-blockers safe and beneficial for cocaine intoxicated patients. This is supported by several reviews putting the unopposed \( \alpha \)-stimulation effect up for discussion, by concluding that no difference, or even beneficial effect, was observed for \( \beta \)-blocker receiving CACP or CMI patients, compared to non-\( \beta \)-blocker treated CACP or CMI patients [30,31,32,33].

The simple explanation of the unopposed \( \alpha \)-effect is that cocaine increases catecholamines that stimulate \( \alpha \)-adrenoceptors, causing smooth muscle contraction and coronary vasoconstriction. [31] When non-selective \( \beta \)-blockers are administered, coronary vasoconstriction can be exacerbated [31]. However, there is conflicting evidence regarding the unopposed \( \alpha \)-effect. The 2008 AHA scientific statement [6] advised against \( \beta \)-blocker treatment, referring to several studies that found exacerbated coronary artery vasoconstriction after propranolol administration [35], significantly increased blood pressure after esmolol administration, no improved outcome after labetalol administration and animal studies showing decreased coronary blood flow, and increased mortality after \( \beta \)-blocker treatment. In addition, several more recent studies describe coronary artery vasospasm [36], and increased ACS rates after \( \beta \)-blocker treatment in CACP patients [37] and also larger myocardial infarction [38] and heart failure in cocaine induced ST-elevation myocardial infarction patients [29]. On the other hand, several studies have been published between 2008 and 2019, concluding that \( \beta \)-blockers are not harmful or even beneficial for CACP and CMI patients. A positive effect of \( \beta \)-blockers for CACP and CMI patients [31,33,38–41], most likely due to \( \beta \)-blocker induced decreased heart rate, blood pressure and ventricular contraction and thereby reduced myocardial oxygen demand and improved outcome. A higher baseline cardiovascular risk [40,41], and a lower incidence of myocardial infarction [38] was found in \( \beta \)-blocker treated CACP patients. Also, \( \beta \)-blocker treated CMI patients had a lower blood pressure [36], and improved long-term survival [39,42], as do cocaine induced heart failure patients [43,44]. Therefore, we suggest that the strong advice against \( \beta \)-blocker use for CACP and CMI patients should be reconsidered in future scientific statements and guidelines. Labetalol [33] and metoprolol might be beneficial [33], and \( \beta \)-2-blocking agents should be avoided [31,33]. Currently, potentially more effective cocaine use disorder treatment options are in the pre-clinical and clinical development stage. [45,46] These treatments are based on accelerating cocaine metabolism by administering a cocaine hydrolase (CocH) [45]. This cocaine metabolizing enzyme is able to rapidly reverse cocaine toxicity and has already been tested in rats [45]. Further studies need to be done developing these enzymes, that can potentially be promising.

Follow-up for CACP patients was more commonly organised by cardiologists. This difference might be due to the different a priori probability of coronary artery disease in emergency department and coronary care unit patients. Chest pain as a result of cocaine use is generally caused by sympathomimetic stimulation, which is transient. Few studies are available on this topic and no advice on the necessity of
follow-up for CACP can be given at this moment. However, chronic cocaine users are more prone to developing structural underlying pathology, such as atherosclerosis and cardiomyopathy, which justifies follow-up with coronary imaging. [47] In order to provide proper drug counselling and treatment, drug testing of hair samples can be considered. [48]

5. Limitations

There are limitations to this study that might have caused an over-estimation of the respondents' knowledge of CACP. Obviously, addressing the question of cocaine implies that this is a relevant risk factor for ACS. Another cause might be the fact that responders are mainly from teaching hospitals. The study was performed in 2015–2016, but since the AHA guidelines and ESC ACS guidelines have not changed on this matter, we are confident that the results of this study are still relevant. An underestimation of CACP knowledge is not expected. We recommend further research on the knowledge, diagnostics and treatment of CACP outside the Netherlands, on the validity of the ESC ACS guideline for CACP patients and validity of risk stratification scores for the use of cocaine.

6. Conclusion

The current practice for CACP patients in most emergency departments and coronary care units in the Netherlands is not in line with the 2008 AHA scientific statement. Emergency physicians and cardiologists should be advised to routinely question all chest pain patients on drug history, and be aware that the routinely used risk stratifications scores are not validated for CACP. Despite the AHA scientific statement, many respondents utilize β-blockers for CACP patients, which is supported by published evidence since the statement appeared. The authors kindly suggest the evaluation and treatment for CACP patients to be added to future guidelines, and to revise and update the AHA scientific statement on this topic to incorporate current practice patterns and evidence-based literature regarding the safety and benefit of β-blockers for CACP and cardiomyopathy.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxrep.2020.12.011.

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