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Review Article

Emerging Role of Coronary Computed Tomography in Non-ST Elevation Acute Coronary Syndrome

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Abstract
NSTEACS is subset of ACS that may present with a wide degree of stenosis from normal vessels to severe obstruction. Identification of which population of NSTEACS that has normal vessels has attracted a great attention. Several trials on non-invasive imaging such as coronary computed tomography have been largely investigated. Current available trials have showed that coronary computed tomography is accurately identify significant stenosis in patients with NSTEACS thus can be used to rule out the disease and reduce the need and duration of unneeded antithrombotic. However, several limitations of the studies has to be taken into account when translating into clinical practice. Nevertheless, current evidence are showing promising results on the role of coronary computed tomography in management of NSTEACS.

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Introduction

Patients with NSTEACS may present with a wide range of stenosis from normal vessels to severe obstruction in coronary angiography. Current guideline still recommends to perform a diagnostic angiography in patients with NSTEACS based on its risk stratification. However, routine angiography may cause significant risk and needs a high resources.[1] During prolonged waiting for diagnostic angiogram, patients often has been administered with prolonged antithrombotic and anticoagulant, which provide no benefit in patients with non-significant stenosis but do increase bleeding risk. Not only did angiogram available only in few number of hospitals but also angiogram is prioritized for patients with ST-elevation myocardial infarction (STEMI) which resulted in more delay on decisive treatment for patients with NSTEACS. Several study on non-invasive imaging have been conducted to answer this problem. Widespread use of coronary computed tomography in routine daily practice has caused several investigators to seek the role of coronary computed tomography in the setting of acute coronary syndrome, especially in NSTEACS. In this review, current progress and recommendation regarding the role of coronary computed tomography in NSTEACS is provided.[2]

Wide Range of Obstruction in NSTEACS

NSTEACS is subset of acute coronary syndrome that characterized by inconclusive ECG changes with no persistent ST segment elevation which can be divided into NSTEMI and unstable angina. Patients with NSTEACS is heterogeneous group whose the range obstruction may vary from normal vessel to heavy stenosis. Several studies in recent past years have demonstrated that patients with NSTEACS have consistently showed a proportion of no significant stenosis. The rate of non-significant stenosis is vary among studies, likely due to difference on diagnostic criteria. CRUSADE registry showed that 8.6% of 38,301 patients with NSTEMI from angiography. Several other trials also reported about 9-12% rate on non-significant stenosis in NSTEACS.

Another interesting findings from SWEDEHEART registry regarding the use of high sensitivity of troponin T in the diagnosis can also give some insight about the variable degree of obstruction in NSTEACS. In SWEDENHEART registry involving 48,594 patients, the analysis that divided the population based on its hs-cTnT levels (using Elecys troponin T, Roche) into four groups : hs-cTnT <6 ng/mL, 6-13 ng/mL, 14-49 mL, and > 50 ng/mL which correspondence into ESC recommended assay specific cut-off levels for very low, low, moderate, and high respectively. Although the analysis did not included dynamic changes of hs-cTnT, which may provide better information on ongoing process of myocardial infarction in coronary obstruction, the result of analysis give some insight on various etiologies of elevated cardiac enzyme. The percentage of non-significant coronary disease based on current ESC term for very low hs-cTn have a proportion normal angiography of 56.8%, low of 39%, "other" of 28.6%, and high of 12%. Current ESC guideline recommends to observe the "other" level of hs-cTnT which may contribute to prolonged course of antithrombotic or anticoagulant on this group which may be caused by other etiologies other than coronary artery disease.

There are several conditions that associated with elevated troponin levels are tachyarrhythmia, heart failure, hypertensive emergencies, critical illness (sepsis, burn), myocarditis, Takotsubo syndrome, valvular disease, aortic dissection, acute neurological event.[4] The fate of this particular group (non-obstructive NSTEACS) is also not quite good. Based on ACUITY trial evaluating the prognosis of non-obstructive NSTEMI and obstructive NSTEMI, the mortality rate of non-obstructive NSTEMI compared to obstructive STEMI is not significantly different at 1-month and 1-year. The most common cause of non-obstructive death NSTEMI in the study was non-cardiac cause with no significant difference of major bleeding from obstructive NSTEMI case indicating the side effect of prolonged unnecessary antithrombotic in this group.

Role of Coronary Computed Tomography in NSTEACS

Coronary angiography for NSTEACS is a widely used tools in managing ACS patients. It reveals the presence of significant coronary stenosis that needs revascularization. However, in limited areas or centers with high load of cases, diagnostic work up of NSTEACS is often delayed and patients can posed to unnecessary treatment. Recent meta-analysis from

13 trials with 164,225 participants showed that there aspirin use in patients without cardiovascular disease does lower the risk for major cardiovascular events by 11% (HR 0.89, ARR 0.41%) but significantly increased risk of major bleeding by 43% (HR 1.43 ARR 0.47%). This implicate that in patients with normal coronary vessels, DAPT strategy did not recommended.[5]

Non-invasive imaging such coronary computed tomography angiography has been a largely investigated tools on its role in coronary artery disease. Coronary computed tomography has a high diagnostic accuracy for the detection of obstructive. There were at least 3 trials to date published regarding the role of coronary computed tomography in NSTEACS: CARMENTA, VERDICT trial, and Kuhl et al. CARMENTA trial was a 3-arm, prospective, open label, single center, randomized controlled, comparative trial using CMR and coronary computed tomography as a gatekeeper to coronary angiography in patients with NSTEACS. The study recruited 207 patients in which 69 patients assigned to routine clinical care, 68 were assigned to CMR first, and 70 were assigned to coronary computed tomography first. Obstructive coronary disease defined by coronary CT as > 70% narrowing of coronary artery or Agatston score >1000 in the absence of extra-cardiac findings (such as aortic dissection or pulmonary embolism). Patients requiring immediate coronary angiography (very high risk feature), non-MI suggestive origin, and previously known CAD was excluded. Follow up coronary angiography performed in all routine clinical care group but only performed in selected cases in CMR and computed tomography groups based on initial CMR or computed tomography coronary result. If the scan was normal, equivocal, non-diagnostic, no formal recommendation was given to undergo ICA. The result of this study was there was significant reduction of coronary angiography in computed tomographyand CMR arm. Coronary angiography use reduced from 100% in routine clinical care to 66% in coronary computed tomography group (p<0.001) and to 87% in CMR group (p<0.001). This protocol appeared to be safe that there was no significant increase of major cardiovascular events in coronary computed tomography first protocol compared to routine clinical care in 350 days follow up (HR 0.64 (CI95% 0.18-2.27, p=0.49). CARMENTA trial has showed that non-invasive first imaging strategy is safely reduced the need for ICA for NSTEACS.[2]

The same positive result on coronary computed tomography was also published by VERDICT trial. VERDICT trial is a prospective, randomized, and multicenter controlled trial. The study was conducted in 9 hospitals in Denmark with NSTEACS. The inclusion criteria of the study was age > 18 years, clinical suspicion of ACS, and has at least 1 of the high risk criteria (ECG changes indicating new ischemia, and elevated cardiac enzyme). The exclusion criteria was very high risk feature of NSTEACS, expected survival <1 year, and intolerance to platelet inhibitors or X-ray contrast. The study initially recruited 2.147 patients but only 1.822 patients eligible for coronary computed tomography. however, only 1.023 patients were included in the study due to not specific reasons. The result showed that from 1.023 patients, 705 patients (69%) had positive computed tomography result (stenosis >50%), 5 patients (5%) had non diagnostic result, and 265 (26%) had negative result. From this negative computed tomography result, only 24 patients (9.05%) had positive result on coronary angiography and from 705 patients that has positive computed tomography result, 666 (94.46%). This findings implicate that coronary computed tomography has a sensitivity of 96.5% (CI95% 94.9-97.8%), specificity of 72.4% (CI95% 67.2-77.1%), PPV 87.9 (85.3-90.9%), and NPV of 90.9% (86.8-94.1%). They also found that the diagnostic yield of this study is not influenced by clinical risk profile. This highlight important finding that diagnostic performance is not affected by high GRACE score. This findings showed that coronary computed tomography may have a role on NSTEACS cases.[1]

Findings from Kuhl et al6 also showed some positive results. The investigators evaluated the role of 64-detector CCTA presenting with NSTEMI prior to coronary angiography. NSTEMI diagnosis was made based on ESC guidelines and they recruited 400 patients consecutively. The study excluded patients with high risk feature, known renal disease, cardiac arrhythmias, and allergic to iodine contrast. All patients in the study underwent coronary computed tomography and coronary angiography. The study have some positive results that coronary computed tomography can detect significant coronary artery disease (>50%) with a sensitivity, specificity, PPV, and NPV of 99%, 81%, 96%, and 95%. The study also found that coronary

Trial	No. patients	Design	Population	Primary end points	Secondary end points	Main findings	Study limitations
VERDICT trial (2020)[1]	1023	Prospective, observational, randomized, controlled, blinded	NSTEACS, non-very high risk NSTEACS	Ability of coronary computed tomography to rule out significant stenosis (> 50%)	Diagnostic accuracy of coronary computed tomography stratified by randomization groups	Coronary computed tomography has a high diagnostic accuracy to rule out significant stenosis with NPV of 90,9% (95%CI 86.8-94.1%)	Large number of drop out (799 patients) without clear reason, significant stenosis cut-ff of 50%
CARMENTA trial (2019)[2]	207	3 arm (routine clinical care, computed tomography, CMR), randomized, controlled, open label	NSTEMI, non-very high risk NSTEMI	Proportion of patients referred to coronary angiography during initial hospitalization	Occurrence of major adverse cardiovascular events within 1 month and 1 year	Computed tomography first strategy reduced the need of corangiography from 100% to 66% with no significant safety issues	No specific protocol of angiography referral from computed tomography arm (based only independent cardiologist decision)
Kuhl et al[6] (2017)	400	Observational study, consecutive, non-controlled, blinded	NSTEMI, non-very high risk	Coronary CT to triage patients at high risk of CAD	-	Coronary CT detects significant stenosis >50% with sensitivity, specificity, PPV, and NPV of 99%, 81%, 96%, and 95% respectively	Consecutive patients, selection bias

Figure 1. Summary of Randomized Clinical Trials.

computed tomography correctly triage patients in 86% cases into PCI or CABG.

Translation to Clinical Practice

Current ESC recommendation regarding NSTEACS management is still rely on 0/1/3 hs-cTn rule in which patients with very low hs-cTnT or minimal increase of hs-cTnTcan be safely discharged and may be undergo several optional testing such as stress testing, coronary computed tomography, or angiography meanwhile in high hs-cTNT should be admitted to CVCU and underwent angiography based on risk stratification. Patients with very high risk NSTEACS should undergo immediate invasive angiography (<2 h) and in high risk patient in less than 24-h. Patients with low-intermediate risk should be managed according to diagnosis and management of CCS in which non-invasive testing was preferred over invasive strategy.[6]

Coronary angiography strategy provide clarification on whether the angina chest pain originating from culprit lesion or non-coronary origin. However, coronary angiography also possess a procedural and bleeding risk. Multiple RCT and meta-analysis have showed that routine angiography does not reduce all-cause mortality risk in overall populations of NSTEACS thus only performed based on risk stratification. Current ESC recommendation regarding computed tomography coronary was to use computed tomography coronary as an alternative to invasive angiography to exclude ACS when there is low-intermediate likelihood of CAD and when troponin and/or ECG are normal or inconclusive. This recommendation is quite contrast to the findings of VERDICT, CARMENTA, and Kuhn's trial in which computed tomography coronary can accurately identify patients with significant stenosis without increased in safety issues and can be used in NSTEACS case (except very high risk NSTEACS) as a gatekeeper to coronary angiography suggesting the need of better evidence to support the findings of current evidence.[7]

There are some points to needs to be considered interpreting the result of the findings. A large number of participants that excluded in the VERDICT trial

have to be taken into account when interpreting the result. No clear reason on not performing computed tomography scan on those patients may cause selection bias on the study. The stenosis cut-off 50% on Kuhn et al and VERDICT trial and 70% on CARMENTA also maybe provide little information about the effect of the stenosis on myocardial infarction that many investigators presume that 50% stenosis are not hemodynamically significant. Current clinical decision making on revascularization also not only depends on stenosis threshold but also depend on several other criteria such as FFR. Other point that has to be taken into account is the resources used in VERDICT and CARMENTA trial. Coronary computed tomography that was used in VERDICT trial was 320-detector computed tomography and in CARMENTA with second generation dual source computed tomography (128-slice) which can largely affect the result and implementation in clinical practice. Another limitation in the studies mentioned above is the lack of clarity and homogeneity of the diagnosis of NSTEMI or NSTEACS. In VERDICT trial, cardiac enzyme that used in the study is troponin and not a high sensitive troponin T. There are also lack of description on how dynamic changes of hs-cTnT affect the diagnosis of NSTEACS which was fundamental.[6,7]

Despite several limitations, the findings from the 3 studies showed that there may be a role of coronary computed tomography on NSTEACS. Current study showed that coronary computed tomography can be helpful in the diagnosis of significant coronary disease in NSTEACS and appear to be safe to be taken. However, due to its logistical and safety issues, there is a need for a larger study to evaluate the efficacy and safety of coronary computed tomography in the setting of NSTEACS. Several studies are being conducted such as FFR-CT and CT-NSTEMI trial regarding its issues and may provide better understanding on the role of coronary computed tomography on NSTEACS.

Conclusion

Although there is no clear guidance the usage of coronary computed tomography on high risk NSTEACS, the findings of VERDICT and CARMENTA provide an insight of the future role of coronary computed tomography on NSTEACS. Several trials is being conducted on the role of computed tomography on NSTEACS for a better understanding of its role.

References

1. Linde JJ, Kelbaek H, Hansen TF, Sigvardsen PE, Pedersen computed tomography, Bech J, et al. Coronary computed tomography angiography in patients with Non-ST segment elevation acute coronary syndrome. J Am Coll Cardiol. 2020;75:453-63
2. Smulders MW, Kitsealer BLJH, Wildberger JE, Dagnelie PC, Rocca HPBL, Mingels AMA. Initial imaging guided strategy versus routine care in patients with non-ST segment elevation myocardial infarction. J Am Coll Cardiol. 2019;74:2466-77
3. Melki D, Lugnegard J, Alfredsson J, Lind S, Eggers KM, Lindahl B. Implications of introducting high sensitivity cardiac troponin T into clinical practice. J Am Coll Cardiol. 2015;65:1655-64
4. Collet JP, Thiele H, Barbato E, Bathelemy O, Bauersachs J, Bhatt DL. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation. Eur Heart J. 2020;0:1-79
5. Zheng SL, Roddick AJ. Association of Aspirin use for primary prevention with cardiovascular events and bleeding events : A systematic review and meta analysis. JAMA. 2019;321(3):277-287
6. Achenbach S. Coronary computed tomography angiography : moving up on the risk scale. J Am Coll Cardiol. 2020;75(5):464-6
7. Sullivan JO. Consider a computed tomography angiogram before coronary angiogram in patients with NSTEACS. BMJ Evidence Based Medicine. 2020 Epub ahead of print: 2020. doi:10.1136/bmjebm-2020-111402.