Intravascular lithotripsy for treatment of calcific coronary lesions in ST elevation myocardial infarction

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Abstract

Aims: To describe the utility and safety of intravascular lithotripsy (IVL) in the setting of primary percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI).

Methods and results: We performed a retrospective analysis, across six UK sites of all patients in whom IVL was used for coronary calcium modification of the culprit lesion during primary PCI for STEMI. The 72 patients were included. IVL was used in de-novo culprit lesions in 57 (79%) of cases and culprit in-stent restenoses in 11 (15%) of cases. In four cases (6%) it was used in a newly deployed stent when this was under-expanded due to inadequate calcium modification. Of the 30 cases in which intracoronary imaging was available for stent analysis, the average stent expansion was 104%. Intra-procedural stent thrombosis occurred in one case (1%), and no-reflow in three cases (4%). The 30 day MACE rates were 18%.

Conclusion: IVL appears to be feasible and safe for use in the treatment of calcific coronary artery disease in the setting of STEMI.

KEYWORDS
coronary artery disease, calcium, percutaneous coronary intervention, ST elevation myocardial infarction

1 | INTRODUCTION

Primary PCI is increasingly performed in older and more co-morbid patients,1,2 with more calcified and complex coronary artery disease. Angiographic coronary artery calcium (CAC) is frequent in target lesions in STEMI,3 associated with worsened epicardial flow, a poorer response to fibrinolytic therapy, and is an independent risk factor for increased cardiovascular major adverse events (MACE).4

Existing tools for calcium modification have limitations in STEMI which may restrict their use. Repeated high pressure balloon dilatation in a thrombotic lesion can cause distal embolization. Although data are scarce on the use of rotational atherectomy in STEMI, it is relatively contraindicated due to the risk of no-reflow caused by embolization of atheromatous debris. This risk is likely to be greater in the highly thrombotic milieu of STEMI, where the microvasculature may already be congested. There is also a risk of increased platelet activation by the heat generated...
Coronary intravascular lithotripsy (IVL; Shockwave Medical, CA, USA) is an emerging treatment modality for vascular calcium that may offer advantages over existing therapies. IVL has been shown to be safe and effective in patients with calcific disease requiring revascularization for stable clinical syndromes. \cite{5}

Coronary calcium is a major risk factor for stent underexpansion and subsequent stent failure. \cite{3,6-8} In addition to facilitating optimal stent expansion in de-novo lesions, \cite{5} IVL has demonstrated utility in the management of under-expanded stents due to coronary calcification, \cite{9} and may be of particular use in this subset of patients presenting with STEMI. As a balloon-based therapy, IVL has a reduced learning curve compared to other calcium modification techniques, and with the potential for low complication rates, may have an advantage over these existing tools. \cite{5}

Here we present the first description of procedural characteristics and safety outcomes following IVL use in STEMI.

## METHODS

### Study design and patient population

We performed a retrospective analysis of all patients in whom IVL was used during primary PCI at six UK sites between June 2018 and September 2020. Inclusion criteria were presentation fulfilling criteria for STEMI (chest discomfort or other symptoms suggestive of ischemia and ST segment elevation in at least two contiguous ECG leads) and the use of IVL in the culprit lesion during the primary PCI. All patients received IVL as part of standard care, with therapy administered as per the manufacturer’s recommendations.

### Procedure

Interventional strategy was determined by anatomy and operator preference. Antithrombotic therapy was prescribed according to current guidelines.

### Endpoints

The primary safety endpoint was procedural complications and inhospital major adverse cardiac events (MACE), defined as all-cause death, non-fatal myocardial infarction (MI) or target vessel revascularization (TVR). \cite{10}

### Definitions

An undilated lesion was defined as a lesion which failed to yield despite high pressure (>18 atm) inflation of a non-compliant (NC) balloon sized 1:1 to the vessel. Severe angiographic calcification was defined as radiopacities seen before contrast injection, appearing to involve both sides of the arterial lumen on angiography. Concentric calcium was defined as >270° calcium arc seen on intracoronary imaging. Thrombolysis in Myocardial Infarction (TIMI) criteria was used to describe coronary flow, and has been defined previously. \cite{11} No reflow (TIMI 0–1) was defined as a persistent reduction in coronary flow in the absence of dissection, spasm, stenosis or thrombus of the epicardial vessel. \cite{12} Stent expansion was defined as the minimum stent area (MSA) divided by the distal reference area, expressed as a percentage. Stent underexpansion was defined as stent expansion <90%. Target lesion revascularization (TLR) was defined as repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. \cite{10} Bleeding was defined as BARC Type 3 bleeding. \cite{13} Significant bystander lesions were defined as major epicardial arteries with >70% angiographic stenosis.

### Statistical analysis

Continuous data are expressed as a mean ± SD, categorical data are expressed as total number and percentage unless otherwise stated.

| TABLE 1 | Patient characteristics | All patients (n = 72) |
|----------|-------------------------|----------------------|
| Age, years (SD) | 72.9 (10.9) |
| Male | 85% (61) |
| Hypertension | 64% (46) |
| Diabetes | 22%\textsuperscript{14} |
| Smoking (current/previous) | 53% (38) |
| Renal impairment\textsuperscript{a} | 36% (26) |
| Previous CABG | 4%\textsuperscript{3} |
| Previous PCI | 25%\textsuperscript{15} |
| Statin therapy | 47% (34) |
| Warfarin/DOAC pre-admission | 10%\textsuperscript{7} |
| BMI, kg/m\textsuperscript{2} (SD) | 26.3 (4.8) |
| LVEF<55% | 72% (52) |
| LVEF<35% | 29%\textsuperscript{16} |

Abbreviations: CABG, coronary artery bypass grafting; BMI, body mass index; DOAC, direct oral anticoagulant; LVEF = left ventricular ejection fraction; PCI, percutaneous coronary intervention.

\textsuperscript{a}eGFR<60 ml/min.
RESULTS

We identified 72 eligible patients, over a 2 year period, representing 1% of total STEMI procedures undertaken across the six sites. The total annual STEMI number of the sites is 3,328, the total annual number of PCIs 11,912, and the total annual number of IVL cases 503.

Patient characteristics are shown in Table 1.

Procedural characteristics are shown in Table 2. IVL was used in de-novo culprit lesions in 57 (79%) of cases and culprit in-stent restenoses in 11 (15%) of cases. In four cases (6%) it was used in a newly deployed, under-expanded stent when this was due to inadequate calcium modification. In 71% of cases, IVL was used as the primary treatment for calcium, and in 29% of cases it was used as a secondary modality.

3 | RESULTS

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after the culprit lesion failed to yield to high pressure NC balloon inflation. In 21% of cases, IVL was used in an under-expanded stent (whether a previously or newly placed). In 4%, IVL was used prior to any other calcium modification, based on the presence of concentric calcium seen on intracoronary imaging, and in 4%, the operators elected to use IVL prior to any other calcium modification, because severe calcification was identified on angiography.

Procedural and clinical outcomes are shown in Table 3. Intra-procedural stent thrombosis occurred in one case (1%), and no-reflow in three cases (4%), two of which occurred immediately after delivery of IVL, in cases with TIMI 0–1 flow at the start of the case. The third instance of no-reflow occurred in a patient with initially TIMI 3 flow, following repeated high pressure inflations with an NC balloon (prior to IVL). 30-day all-cause death occurred in 12 (17%) of patients. There was one case of repeat infarction requiring TVR, due to stent thrombosis of an inadequately expanded stent (due to inadequate calcium
Intravascular ultrasound (IVUS) demonstrating calcified nodule. As CAC increases with age,21 the incidence of calcific capped lipid rich plaque, in 8% of STEMI the culprit lesion is an eroded STEMI.

This retrospective analysis describes the procedural characteristics and safety outcomes in patients treated with IVL during STEMI.

Although STEMI is most commonly caused by rupture of thin capped lipid rich plaque, in 8% of STEMI the culprit lesion is an eroded calcified nodule. As CAC increases with age,24 the incidence of calcification (54%) within all STEMI19 and eroded calcific nodules are also likely to increase. Dealing with CAC in the context of STEMI may carry a higher risk of procedural complications and, if CAC is inadequately treated, a higher risk of stent failure. Existing technologies such as high pressure balloon inflation, scoring or cutting balloons and rotational atherectomy are associated with increased rates of slow/no reflow, severe dissection and perforation. This may translate to a reluctance to modify calcium within STEMI and explain the low use of these technologies. We hypothesize that these risks may be reduced with IVL, due to the low pressure inflations used (4-6 atm) and the absence of distal embolization of calcific remnants.14 Our findings were consistent with this hypothesis and demonstrated low rates of procedural complications or inpatient adverse events. Rates of no-reflow were low (4%, compared to reported rates of 20-30%17,22) with no cases of perforation reported in keeping with safety rates previously published for IVL.23 The low incidence of no-reflow may reflect a lower need for repeated high pressure balloon inflation to achieve lesion expansion.

Coronary angiography is insensitive for the diagnosis of CAC which may explain the high incidence of intravascular imaging within our cohort (55%, compared to 2.7% in a large US registry of all acute myocardial infarctions, and compared to 9% in all PCI in the UK. (20, 21)). Intravascular imaging is a sensitive way of identifying the need for calcium modifying therapies and assessing both the response to therapy and the final stent result. Of the 29 cases in which intracoronary imaging was performed prior to IVL, there was an average calcium arc of 314°, indicating appropriate use of IVL. One such representative case is shown in Figures 1-5. A further potential advantage of IVL is the ability to modify deep wall and/or medial coronary calcium and thereby restore vessel compliance, this may in turn translate into larger MSAs and a lower incidence of stent failure. Indeed, of the 30 cases in which intracoronary imaging was available for stent analysis, the average stent expansion was 104%, indicating satisfactory mechanical results achieved in these heavily calcified lesions. The 30 day mortality rate of this cohort was 17%, significantly higher than 30 day mortality rates for STEMI of 9% from both UK and Swedish national registries.2,25 Of the 12 deaths, eight were cardiac
deaths, and all due to cardiogenic shock or ventricular arrhythmia in patients with severe LV impairment, most of whom were older than 80 years. The non-cardiac deaths included one due to hypoxic brain injury complicating out of hospital arrest, two were due to malignancy and one perforated cholecystitis.

Although this study is limited by the lack of control group and modest sample size, it provides a “real-world” demonstration of the utility and safety of IVL use in STEMI and adds to the growing body of evidence of the important role of IVL in coronary calcium modification.

5  |  CONCLUSION

In the setting of primary PCI for STEMI, IVL appears to be a safe and effective tool for modification of calcified coronary lesions prior to stent implantation.

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DATA AVAILABILITY STATEMENT

Data available on request from the authors: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Hall M, Laut K, Dondo TB, et al. Patient and hospital determinants of primary percutaneous coronary intervention in England. 2003–2013. Heart. 2016;102(4):313-319. https://doi.org/10.1136/heartjnl-2015-308616.
2. National Institute for Clinical Outcomes Research. Myocardial ischaemia national audit project. 2019 Summary Report 2019.
3. Généreux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndrome: pooled analysis from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) and ACUITY (acute catheterization and urgent intervention triage strategy) TRIALS. J Am Coll Cardiol. 2014;63(18):1845-1854. https://doi.org/10.1016/j.jacc.2014.01.034.
4. Kirtane AJ, Kosmidou I, Karmpaliotis D, et al. Association of culprit lesion calcium with angiographic and clinical outcomes in patients with ST-elevation myocardial infarction treated with fibrinolytic therapy. Am J Cardiol. 2005;95(3):337-342. https://doi.org/10.1016/j.amjcard.2004.09.030.
5. Ali ZA, Nef H, Escaned J, et al. Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary Stenoses: the disrupt CAD II study. Circ Cardiovasc Interv. 2019;12(10):e008434. https://doi.org/10.1161/circinterventions.119.008434.
6. Mintz GS. Intravascular imaging of coronary calcification and its clinical implications. JACC Cardiovasc Imaging. 2015;8(4):461-471. https://doi.org/10.1016/j.jcmg.2015.02.003.
7. Prati F, Kodama T, Romagnoli E, et al. Suboptimal stent deployment is associated with subacute stent thrombosis: optical coherence tomography insights from a multicenter matched study. From the CLI foundation investigators: the CLI-THRO study, Am Heart J. 2015;169(2):249-256. https://doi.org/10.1016/j.ahj.2014.11.012.
8. Armstrong EJ, Kwa AT, Yeo KK, et al. Angiographically confirmed stent thrombosis in contemporary practice: insights from intravascular ultrasound. Catheter Cardiovasc Interv. 2013;81(5):782-790. https://doi.org/10.1002/ccd.24460.
9. Yeoh J, Cottens D, Cosgrove C, et al. Management of stent underexpansion using intravascular lithotripsy-defining the utility of a novel device. Catheter Cardiovasc Interv. 2021;97(1):22-29. https://doi.org/10.1002/ccd.28715.
10. García-García HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the academic research Consortium-2 consensus document. Circulation. 2018;137(24):2635-2650. https://doi.org/10.1161/circulationaha.117.029289.
11. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med. 1985;312(14):932-936. https://doi.org/10.1056/nejm1985043121437.
12. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). J Am Coll Cardiol. 2015;66(4):403-469. https://doi.org/10.1010/jacc.2014.12.018.
13. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation. 2011;123(23):2736-2747. https://doi.org/10.1161/circulationaha.110.099449.
14. Ali ZA, Brinton TJ, Hill JM, et al. Optical coherence tomography characterization of coronary Lithoplasty for treatment of calcified lesions: first description. JACC Cardiovasc Imaging. 2017;10(8):979-906. https://doi.org/10.1016/j.jcmg.2017.05.012.
15. Toma M, Buller CE, Westerhout CM, et al. Non-culprit coronary artery percutaneous coronary intervention during acute ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. Eur Heart J. 2010;31(14):1701–1707. https://doi.org/10.1093/eurheartj/ehq129.
16. Ludman P. British cardiovascular intervention society audit data 2018. British Cardiovasc Intervention Soc. 2019:1-1.421.
17. Yang L, Cong H, Lu Y, Chen X, Liu Y. Prediction of no-reflow phenomenon in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Medicine (Baltimore). 2020;99(26):e20152. https://doi.org/10.1097/md.00000000000020152.
18. Park DW, Clare RM, Schulte PJ, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. Jama. 2014;312 (19):2019-2027. https://doi.org/10.1001/jama.2014.15095.
19. Higuma T, Soeda T, Abe N, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. JACC Cardiovasc Interv. 2015;8(9):1166-1176. https://doi.org/10.1016/j.jcin.2015.02.026.
20. Vallabhajosyula S, El Hajj SC, Bell MR, et al. Intravascular ultrasound, optical coherence tomography, and fractional flow reserve use in acute myocardial infarction. Catheter Cardiovasc Interv. 2020;96(1):E59-e66. https://doi.org/10.1002/ccd.28543.

21. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the multi-ethnic study of atherosclerosis (MESA). Circulation. 2006;113(1):30-37. https://doi.org/10.1161/CIRCULATIONAHA.105.580696.

22. Morishima I, Sone T, Okumura K, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol. 2000;36(4):1202-1209. https://doi.org/10.1016/s0735-1097(00)00865-2.

23. Hill JM, Kereiakes DJ, Shlofmitz RA, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease: the disrupt CAD III study. J Am Coll Cardiol. 2020;76(22):2635-2646. https://doi.org/10.1016/j.jacc.2020.09.603.

24. Muller DW, Topol EJ, Ellis SG, Sigmon KN, Lee K, Califf RM. Multi-vessel coronary artery disease: a key predictor of short-term prognosis after reperfusion therapy for acute myocardial infarction. Thrombolysis and angioplasty in myocardial infarction (TAMI) study group. Am Heart J. 1991;121(4 Pt 1):1042-1049. https://doi.org/10.1016/0002-8703(91)90661-z.

25. Szummer K, Wallentin L, Lindhagen L, et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. Eur Heart J. 2018;39(42):3766-3776. https://doi.org/10.1093/eurheartj/ehy554.

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