Management and outcomes of significant non-culprit coronary artery lesions in STEMI: a retrospective cohort study

Robert E.M. Weitemeyer¹, Shane P. Murphy², Ruth Gillen³, Catriona Ahern⁴, Yousif Abusalma⁵, Hatim A. Yagoub⁶, Bryan P. Yan⁷, Andrew E. Ajani⁸, Ailish Hannigan⁹, Tom J. Kiernan¹⁰

¹. University of Limerick, Graduate Entry Medical School, Castletroy, Co. Limerick, Ireland. rob.weitemeyer@gmail.com
². University of Limerick, Graduate Entry Medical School, Castletroy, Co. Limerick, Ireland. shanepetermurphy@gmail.com
³. University of Limerick, Graduate Entry Medical School, Castletroy, Co. Limerick, Ireland. gillenr@tcd.ie
⁴. University Hospital Limerick, Department of Cardiology, Dooradoyle, Co. Limerick, Ireland
⁵. University Hospital Galway, Newcastle Road, Galway City, Co. Galway, Ireland
⁶. University Hospital Limerick, Department of Cardiology, Dooradoyle, Co. Limerick, Ireland. drhatimyagoub@yahoo.com
⁷. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
⁸. Department of Cardiology and Cardiac Surgery, Royal Melbourne Hospital, Melbourne, Victoria, Australia Centre of Cardiovascular Research & Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia. University of Melbourne, Melbourne, Victoria, Australia
⁹. University of Limerick, Graduate Entry Medical School, Castletroy, Co. Limerick, Ireland. ailish.hannigan@ul.ie
¹⁰. University Hospital Limerick, Department of Cardiology, Dooradoyle, Co. Limerick, Ireland

University of Limerick, Graduate Entry Medical School, Castletroy, Co. Limerick, Ireland. tom_kiernan@hotmail.com

Abstract

Background
In the setting of ST-elevation myocardial infarction (STEMI) and multi-vessel disease (MVD), guidelines recommend revascularization of the culprit lesion (CL) only, due to poor evidence supporting intervention in non-culprit lesions (non-CLs) during the same index procedure. Debate over management for significant non-CLs is of interest i.e. medical management vs. percutaneous revascularization. We describe a cohort of patients with STEMI and MVD and compare the occurrence of major adverse cardiac events (MACE) by therapeutic strategies for non-CLs with regard to follow-up outcomes.

Methods
86 patients with STEMI and MVD were identified from a database of STEMI presentations to the University Hospital Limerick from Jan 2011 to April 2013. The occurrence of MACE was established by follow up with patients’ general practitioners.

Results
48% of presentations had MVD. Predominant management for non-CLs was medical therapy alone comprising 58% (n=50) of patients, while 23% (n=20) of patients underwent PCI for non-CL, and 19% (n=16) had CABG.

Median follow up was 1.8 years (range 9–36 months). We found no significant difference in the occurrence of MACE between medical management of non-CLs and PCI of non-CLs (OR 1.10 95%CI 0.34, 3.56; p= 0.88). CABG however does show a trend to be superior to both PCI (OR 3.10 95%CI 0.54, 17.88; p= 0.21) and medical management (OR 2.83 95%CI 0.65, 12.27; P= 0.17) in non-CLs.

Conclusions
CABG appears superior to both PCI or medical management in preventing MACE over time, and PCI is not superior to medical management alone.

Abbreviations: CL culprit lesion; non-CL non-culprit lesion; MVD multi-vessel disease; MACE Major Adverse Cardiac Event; PCI percutaneous coronary intervention; MV-PCI multi-vessel PCI

Key words: ST-elevation myocardial infarction; STEMI; multivessel disease; non-culprit lesions; percutaneous coronary intervention

Introduction

The presence of multivessel disease (MVD) in patients with ST-segment elevation myocardial infarction (STEMI) is a well recognised prognosticator of poor clinical outcome.1-4 Between 30-50% of STEMI presentations are found in the setting of MVD.5,10 Establishing the most effective treatment strategies in this clinical scenario is therefore important both because it constitutes a large proportion of STEMI presentations, and because of the high risk for poor prognosis.

Reperfusion of the infarct culprit lesion (CL) by primary percutaneous coronary intervention (PPCI) is the standard of care for acute STEMI.11-14 Currently there is debate regarding management strategy for angiographically significant coronary artery lesions neighboring the CL but not implicated in the infarct i.e. a non-culprit lesion (non-CL). Practice guidelines from both the European Society of Cardiology (ESC) and the American Heart Association (AHA) do not endorse reperfusion of significant non-CLs except in the circumstance of cardiogenic shock and persistent ischemia after PCI (ESC), or hemodynamic compromise (AHA).11-14

There is a suggestion that in the current era of drug eluting stents, the current guidelines espousing conservative management of non-CLs is outdated. This refers to the argument that modern drug-eluting stents make the risk of avoiding in-stent restenosis obsolete.

There is controversy in the literature on non-CL management with regard to the prevalence of major adverse cardiac events (MACE). Notably in 2013 the prospective PRAMI study concluded that preventative multi-vessel PCI (MV-PCI) of non-CL lesions incurred a significant benefit to prevention of MACE on follow-up outcome (HR 0.35 95%CI 0.21-0.58).5 Support for this preventative PCI strategy is also found in the prospective study by Politi et al which concluded that medical management of non-CL imparts a significantly higher risk of MACE when compared to multivessel PCI (MV-PCI), and also in the CvLPRIT study which demonstrated a 55% reduction in MACE in those patients presenting for primary-PCI when non-CLs are also stented on the index admission.11,15

However, retrospective studies by both Jaguszewski and Hannan didn’t find a difference in adverse event prevalence between MV-PCI and current guidelines.6,16 Manari et al found that while there was a survival benefit in the long term for MV-PCI this was mitigated by the increased short-term mortality associated with that strategy, ultimately leading to support of current guidelines.9 Additionally there are a number of other studies which support of the current guidelines including Kornowski and Toma.20, 4

The primary aim of this retrospective cohort study is to compare the occurrence of major adverse cardiac event (MACE) at follow-up from one geographic center for patients with acute STEMI and MVD by non-CL management strategies which were categorised as; medical management only, PCI, or CABG. Secondary aims are to describe demographic and angiographic characteristics of this cohort.

Methods

We retrospectively analyzed a cohort of patients with STEMI and MVD from a database of sequential STEMI presentations to the University Hospital Limerick (UHL) in the period from January 2011 to April 2013 from the records of the Cardiac Rehabilitation Unit at the UHL.

Inclusion criteria were: 1) STEMI diagnosis from the records of the Cardiac Rehabilitation Unit at UHL, 2) the patient received coronary angiography at presentation with STEMI and was diagnosed with MVD defined as ≥70% stenosis of ≥2 epicardial coronary arteries or of a main branch. Exclusion criteria were: 1) single vessel disease, 2) angiographic review revealing diagnosis other than STEMI (eg Takotsubo cardiomyopathy), 3) angiographic data unavailable, 4) follow-up data unavailable. All patients received the standard of care as mandated by international guidelines which included appropriate care on acute admission, revascularisation therapy, and coronary care medical management on discharge.12

Demographic characteristics extracted from the hospital records included medications on admission, risk factors present (diabetes mellitus, hypertension, dyslipidemia, history of smoking, history of cardiovascular disease, family history of cardiovascular disease), and general practitioner (GP) contact information. Data on later readmissions and subsequent deaths were also collected. Where referral for coronary artery bypass graft (CABG) existed the review of records was used to confirm that the CABG procedure had occurred.

Coronary catheterization lab data as recorded by the lab system (General Electric) and recorded echocardiograms were reviewed by a board certified cardiologist. Angiographic success was recorded as defined by Thrombolysis In Myocardial Infarction (TIMI) flow score of 3 or 0.16 Data was collected on presenting disease characteristics, TIMI flow, and left ventricular ejection fractions (EF). Data on subsequent PCI procedures was also recorded.

A follow-up questionnaire was distributed to the patients’ own GPs to establish the occurrence of study endpoints; major adverse cardiac events (MACE), and all-cause mortality. MACE is defined as acute coronary syndrome, new onset heart failure, or death (cardiac related). GPs were contacted by surface mail, telephone, and fax. Non-responders were contacted a maximum of 3 times; in March, April, and June of 2014. Patient characteristics (age, gender, eligibility for government-funded free medical care and disease presentation) were compared for those with and without follow-up data to establish if there was response bias.

The main objective of the study was to evaluate revascularisation strategies for non-CLs in patients with STEMI and MVD based on follow-up outcomes. The cohort was classified as follows to assess mechanical revascularisation strategies when compared to medical management of non-CLs; 1. PCI to the CL with medical management of the non-CL; 2. PCI to the CL with any PCI to non-CL (including both primary and staged procedures)

3. Angiographic referral for CABG and subsequent bypass surgery

This study protocol was approved by the Health Services Executive (HSE) Mid-Western Regional Hospital Research Ethics Committee before data collection began and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical Methods

Statistical analysis was performed using SPSS 21 (SPSS, Inc., Chicago, IL). The association between categorical variables was tested using the chi-squared test. Means were compared across two groups using an independent samples t test.

Odds ratio and 95% was calculated for each treatment group.
Statistical regression was used to correct for age and gender.

**Results**

**Demographics and medical history**

Of the 245 patients with a STEMI presentation between January 2011 and April 2013, 215 had full angiographic records, and 211 of these STEMI diagnoses were confirmed by angiogram (4 were not STEMI). MVD was present in 105 (49.8%), however 19 cases were missing follow-up questionnaire data. 86 patients met the inclusion criteria. The majority of these were male (74.4%), with a mean age of 62.9 years (range 36-87 years). There was a high prevalence of traditional cardiovascular risk factors including positive smoking history (61.3%), and positive family history of coronary artery disease (64.5%). 57% of the cohort was eligible for government funded free medical care (national figure 43%). Demographic and risk factor profiles of the cohort are tabulated in Table 1.

**Angiographic description**

The vessels most frequently associated with CLs on coronary angiogram are the right coronary artery (46.5%) and the left anterior descending artery (34.9%). CL severity as measured by percent artery stenosis was almost equally divided: two classification categories; 70-99% occlusion (TIMI flow=3) (51.2%), and 100% occlusion (TIMI flow=0) (48.8%). The most common vessels for significant non-CLs were the circumflex artery (36.3%) and the left anterior descending artery (33.3%). 50% of this MVD cohort presented with more than a single non-CL. Full angiographic characteristics of the cohort are tabulated in Table 2.

Culprit lesions were predominantly managed by PCI (73%, n=63), with the remainder requiring coronary artery bypass graft (19%, n=16), or receiving medical therapy only for clinical reasons (8%, n=7). The predominant management practice for non-CLs was medical therapy alone comprising 58% (n=50) of patients, while 23% (n=20) of patients underwent PCI for non-CL, and 19% (n=16) required coronary artery bypass graft surgery (figure 1). Drug eluting stents were used predominantly with only 3 bare metal stents identified in angiography reports.

**Table 1: Risk factors (n=62 due to incomplete records)**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/o previous PCI/CABG</td>
<td>8</td>
<td>12.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27</td>
<td>43.6%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25</td>
<td>40.3%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>10</td>
<td>16.3%</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>40</td>
<td>64.5%</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoked</td>
<td>38</td>
<td>61.3%</td>
</tr>
<tr>
<td>Current smoker at STEMI</td>
<td>25</td>
<td>40.3%</td>
</tr>
<tr>
<td>Ex-smoker at STEMI</td>
<td>13</td>
<td>21.0%</td>
</tr>
</tbody>
</table>

**Table 2: Coronary angiographic findings (n=86)**

<table>
<thead>
<tr>
<th>Location of culprit lesion</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right coronary artery</td>
<td>40</td>
<td>46.5%</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>30</td>
<td>34.9%</td>
</tr>
<tr>
<td>Circumflex artery</td>
<td>11</td>
<td>12.8%</td>
</tr>
<tr>
<td>Left main artery</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td>Graft</td>
<td>2</td>
<td>2.3%</td>
</tr>
<tr>
<td>Narrowing of culprit lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% - 99%</td>
<td>44</td>
<td>51.2%</td>
</tr>
<tr>
<td>100%</td>
<td>42</td>
<td>48.8%</td>
</tr>
<tr>
<td>Culprit Lesion TIMI flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 0 before PCI</td>
<td>42</td>
<td>49.4%</td>
</tr>
<tr>
<td>TIMI 3 before PCI</td>
<td>33</td>
<td>38.8%</td>
</tr>
<tr>
<td>TIMI 0 after PCI</td>
<td>7</td>
<td>8.8%</td>
</tr>
<tr>
<td>TIMI 3 after PCI</td>
<td>70</td>
<td>87.5%</td>
</tr>
<tr>
<td>Number of Non-Culprit Lesions per patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>50.0%</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>33.7%</td>
</tr>
<tr>
<td>&gt;2</td>
<td>14</td>
<td>16.3%</td>
</tr>
<tr>
<td>Location of Non-Culprit Lesion locations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=119 non-CLs in 76 patients with MVD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>45</td>
<td>33.3%</td>
</tr>
<tr>
<td>Circumflex artery</td>
<td>49</td>
<td>36.3%</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>35</td>
<td>25.9%</td>
</tr>
<tr>
<td>Ramus</td>
<td>6</td>
<td>4.4%</td>
</tr>
<tr>
<td>Narrowing of Non-Culprit Lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% - 70%</td>
<td>48</td>
<td>35.6%</td>
</tr>
<tr>
<td>70% - 99%</td>
<td>78</td>
<td>57.8%</td>
</tr>
<tr>
<td>100%</td>
<td>9</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

**Medical management**

Standard medical management for acute coronary syndrome was used in the majority of cases as outlined in table 3 with the exception of contraindications including aspirin, P2Y12 receptor inhibitor, beta blocker, statin, and either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. Anticoagulation during percutaneous intervention was primarily by heparin alone, and in 43.9% of cases heparin was used in combination with a glycoprotein IIb/IIIa inhibitor.
Table 3: Medical management (n=57 due to incomplete records)

<table>
<thead>
<tr>
<th>Medical management</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>56 (98.3%)</td>
</tr>
<tr>
<td>Plavix/other antiplatelet agent</td>
<td>53 (93.0%)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>51 (89.5%)</td>
</tr>
<tr>
<td>Statin</td>
<td>54 (100.0%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>37 (64.9%)</td>
</tr>
<tr>
<td>ACE-I</td>
<td>41 (71.9%)</td>
</tr>
<tr>
<td>ARB</td>
<td>6 (10.5%)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>47 (82.4%)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>25 (43.9%)</td>
</tr>
</tbody>
</table>

Follow-up Outcomes

82% of GPs in the MVD group completed the follow-up questionnaire. There were no significant differences in the patient characteristics (age, gender, eligibility for free medical care, or disease presentation) of those with follow up or not. Median length of follow up was 1.8 years (range 9-36 months). At follow-up the occurrence of MACE was 36.1% (n=31). MACE is a combined endpoint and in this cohort, the 31 patients suffering MACE included 9 cases of acute coronary syndrome, 9 cases of congestive heart failure, and 15 deaths. While some patients met more than one criteria for MACE, only a single event was recorded per patient for analysis.

Non-CL management strategy was not a significant predictor of MACE after adjusting for age and gender. We found no significant difference in the occurrence of MACE between medical management of non-CLs and PCI of non-CLs (OR 1.10 95%CI 0.34, 3.56; p= 0.88). CABG however does show a trend to be superior to both PCI (OR 3.10 95%CI 0.54, 17.88; p= 0.21) and medical management (OR 2.83 95%CI 0.65, 12.27; P= 0.17) in non-CLs. Raw figures and this comparative analysis is shown in table 4.

Discussion

In this cohort of patients presenting with STEMI and MVD, the prevalent strategy for non-CLs was medical management alone. We found no significant difference in the occurrence of MACE in this cohort between medical management of non-CLs and PCI of non-CLs; indicating non-superiority of either strategy. There is a trend for intervention in the form of CABG to be superior to both PCI and medical management in non-CLs, supporting CABG as the gold standard modality of treatment for multivessel disease.

Meta-analysis by Valaar in 2011, and by Zhang in 2014 both
support current guidelines when comparing against MV-PCI in long term outcome as determined by risk of MACE (Valaar [HR 0.61, 95% CI 0.49-10.77], Zhang [HR 0.50, 95% CI 0.32-0.77]).21, 8 It is notable in these meta-analysis that the majority of this work have been retrospective observational studies. However meta-analysis by Prandit in 2013 which limited inclusion criteria to randomized controlled trials found that stenting significant non-CLs may reduce the risk of death from cardiovascular causes [pooled OR 0.39, 95% CI 0.18-0.83].22 In the light of global controversy in this debate the current study sought to identify outcomes by non-CL management strategy for one geographic area both to inform local practice and to contribute to the growing body of evidence on the issue. The non-superiority of MV-PCI over current guidelines in terms of comparing prevalence of MACE supports the general policy suggested by the Widimski and Holms literature review; single vessel PCI should be the default, MV-PCI should be used only if justified by clinical scenario (such as multiple >90% potentially unstable lesions), and significant MVD should be managed by either medical management to non-CL or by staged PCI to non-CL.23

This ultimately supports the consideration of MV-PCI on a case-by-case basis at this time. In the broader deliberation of future guidelines for MV-PCI follow-up outcomes in terms of MACE will be the primary determinant. However additional consideration should also be lent to non-cardiac side effects of these procedures such as contrast induced nephropathy, and risk of cancer due to increased fluoroscopic time. Furthermore in a budgetary climate consideration is also owed to efficient resource allocation weighed against clinical benefit.

The risk of non-cardiac side effects

It is commonly observed that all-cause mortality includes adverse events not associated with the coronary artery disease but rather associated with the procedure. One of the tenets of the conservative management of non-CLs is the concern over unnecessary risk involved with an extended index procedure at the time of acute STEMI revascularization.11-13 Placing multiple stents requires a longer procedure increasing risks associated with both contrast load and fluoroscopic time.

It is known that exposure to low dose ionizing radiation during cardiac imaging is associated with an increased risk of cancer; a dose dependant relationship of 3% increased 5-year cancer risk for every 10mSv of exposure has been suggested.23, 24 Equally the risk of post procedural glomerular filtration rate (GFR) impairment due to high contrast load is well established.25 One study found that MV-PCI extended the index procedure fluoroscopy time from 11.5 min (690 sec) to 16.2 min (972sec) (1.41 times more exposure), and increased contrast volume to 255ml compared to 200ml for a single vessel procedure.25

Interestingly in-patient analysis of MV-PCI versus CL-only PCI, even in cases of cardiogenic shock, is not associated with increased in-hospital mortality, but was associated with increased bleeding risk (6.7% vs 5.3% p<0.01).26 While post procedural GFR impairment due to contrast load is a topical subject in its own right, this might suggest that the increased contrast load does not cause significant mortality. Concrete conclusions on cancer risk due to low dose ionizing radiation is also a subject of substantial ongoing interest but will require very long term follow-up analysis.

Economic considerations

There are suggestions on both sides of the CL-only versus MV-PCI debate which predict improved allocation of resources. Many of those studies which conclude that MV-PCI confers a survival benefit suggest that revascularization of multiple lesions during the index procedure would be economically advantageous because of lower costs in performing just one procedure for multiple lesions.5, 17

Conversely Di Mario Carlo et al which found MV-PCI to be a safe strategy concluded no economic advantage of MV-PCI when compared to PCI to CL-only in a prospective study which included economic analysis. In the CL-only group the need for subsequent revascularisation due to clinical indication remained low therefore the cost of unnecessary stents was found to be greater than the cost of clinically indicated staged procedures.27

Future development of this research

Current guidelines were constructed including the hypothesis that neighboring lesions on angiogram during acute STEMI may appear to be worse than they actually are due to inflammation caused by the acute infarct.11-13 Functional flow resistance (FFR) studies are now emerging which suggest that the functional stenosis of non-CLs are indeed often over estimated on angiogram after acute STEMI.28

The concept of preventative PCI introduced by PRAMI implies that non-CLs will develop into more serious disease at a later date. Using Intravascular Ultrasound of 99 non-CLs in 63 patients Zhao et al. found a trend towards athrosclerotic evolution of lower risk lesions to higher risk lesions over a 13 month period; including decreased minimum luminal area, and increased size of necrotic core.29

Deeper understanding of the functional implications of significant non-CLs during acute STEMI and an improved knowledge of the natural history of lesion evolution would inform the current debate between MV-PCI and CL-only strategies. Particularly development of FFR data on non-CLs may provide insight to the true functional significance of these lesions versus angiographically determined anatomical significance and provide the case-by-case metric which may be required for this non-CL management debate.

Limitations

This is a small retrospective observational study in one geographical location. Follow up was determined by GP questionnaires instead of, for example, linkage with death certificates. Data from some patients was incomplete. The small sample size resulted in wide confidence intervals for subgroups. Strong response rate in the GP questionnaire does provide confidence in follow-up data due to the proximity of these primary care doctors to patient follow-up outcomes. This study provides reassurance that outcomes at this center are consistent with those reporting globally.

Conclusion

More high quality prospective investigations like PRAMI and CvLPRIT trials are required to provide evidence for the debate between non-CL management strategies. Specifically, comparison between index MV-PCI, staged MV-PCI, and medical management is currently lacking. The results of this study which indicate the non-superiority of MV-PCI compared to medical management of non-CLs is in agreement with guidelines published by both the AHA and the ESC. This is a
common conclusion amongst retrospective studies on this topic however it should be noted that many of the few prospective studies available do support MV-PCI as superior to medical management of significant non-Cls. At this time the narrow difference between these non-CL management strategies does not support a general change to current practice guidelines. However the non-inferiority also demonstrated by this narrow difference also highlights the importance of good clinical decision making to consider if a MV-PCI strategy might have benefit on a patient by patient basis.

Statement of ethical publishing

The authors state that they abide by the statement of ethical publishing of the International Cardiovascular Forum Journal 30

Acknowledgements

The authors express great gratitude for the kind assistance of Teresa Waters in record retrieval. Also thanks to Dr Kevin Johns and Dr Kari-Jean Mckenzie in proof reading.

Address for correspondence:

Robert Weitemeyer*, c/o Prof Tom Kiernan
University Hospital Limerick Dept of Cardiology
Doonaroyal, Co. Limerick
IRELAND
Tel: 001 778 229 5418
E-mail: rob.weitemeyer@gmail.com

*permanent address: 2858 Retallack Street, Regina Saskatchewan, S4S

References