**Missed opportunities in coronary artery disease: reflection on practice to improve patient outcomes**

Running title: Missed opportunities in coronary artery disease

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**Abstract**

Missed opportunities refer to incidents where different actions by those involved could result in more desirable outcomes. While missed opportunities is not an established concept in coronary artery disease (CAD), they are important because CAD is common and potentially life threatening. Treatment of CAD has the potential to prevent poor patient outcomes which can have downstream consequence on resource utilization and costs for healthcare providers. The missed opportunities in CAD could be divided into those related to prevention, early detection, diagnosis and treatment. The primary prevention opportunities include management of patients with risk factors and comorbidities. In terms of diagnosis, a proportion of patients who have underlying CAD are admitted beforehand with symptoms which may be attributed to CAD. However, some may have been misdiagnosed with other conditions and are subsequently readmitted with a delayed diagnosis of ACS. In ACS, there is need for acute treatment and missed opportunities may arise from delay in diagnosis and missed reperfusion therapy. Finally, after coronary revascularization or medication management, there may be missed opportunities for patients related to secondary prevention such as smoking cessation, exercise, weight loss, attendance at cardiac rehabilitation and receipt evidenced based therapies including antihypertensives, antiplatelet and statin therapy. Our review finds that missed opportunities can become apparent if looked for in the care of patients with CAD. While the term is non-specific, it should be contextualized and described as those which are related to prevention, diagnosis and treatment. Only through reflection on clinical activities in relation to patient outcomes and the use of healthcare services can missed opportunities be identified so that better care can be delivered.

**Keywords:** coronary artery disease; acute coronary syndrome; prevention; diagnosis; management

**Introduction**

Missed opportunities refer to incidents where different actions by those involved could result in more desirable outcomes. Essential in this concept is capturing events in sufficient detail and providing objective and unbiased reflection on what could have been changed. In addition, there should be a clear demonstration that a favorable outcome may be achievable had decisions deviated from actual actions. Globally, it has been estimated that ischemic heart disease affects approximately 126 million individuals or 1.72% of the world’s population [[[1]](#endnote-1)]. Small improvements to care by limiting missed opportunities for an individual can have a large population impact if replicated for primary and secondary prevention populations.

The missed opportunities for people with CAD could be divided into those related to prevention, early detection, diagnosis and treatment. Preventative therapies aim to reduce the onset or progression of disease that could result in symptoms and/or cardiac dysfunction. These opportunities include primary prevention, where risk factors are identified and modified to reduce events in healthy populations and secondary prevention after an event with the aim of preventing recurrence and improving other outcomes. Early identification of CAD can allow for measures to be taken to prevent disease progression and minimize risk of adverse outcomes. For diagnostic and treatment related opportunities, suboptimal care may relate to decisions made about choices and timing of diagnosis and therapy. A challenge related to CAD is that it is represents a spectrum of conditions of variable severity, ranging from asymptomatic coronary atherosclerotic disease to acute coronary syndrome (ACS) and interruptions to optimal therapy can have specific consequences for patients and health services. In addition, opportunities may be missed on different levels, such as patients and clinicians in the community who fail to recognize the significance of their symptoms or action (or inaction) by general physicians or cardiology specialists in the outpatient, emergency department and the inpatient settings. These opportunities could relate to misdiagnosis or delayed diagnosis. For therapy, opportunities may be lost due to postponement of treatment and strategy of management as choice of interventions such as percutaneous coronary intervention or coronary artery bypass, antithrombotics and therapies to reduce cardiovascular risk such as cholesterol reducing agents, blood pressure control and lifestyle modification may affect patient outcomes.

An overview of how missed opportunities in the context of CAD has not been evaluated before. In this review, we outline how missed opportunities for CAD has been described in the literature and provide a discussion about important concepts in studying missed opportunities.

*Primary prevention related missed opportunities*

A few studies have evaluated missed opportunities in the primary prevention of CAD. Sheppard et al evaluated cardiovascular disease prevention from primary care settings using a cross sectional study of 34,975 patients from 19 general practices in the UK [[[2]](#endnote-2)]. They showed that 64% of patients eligible for primary prevention therapy were being treated appropriately based on their cardiovascular disease risk and that guideline adherence was highest in patients with ischemic heart disease (52%). An Australian case-control study of 559 participants suggest that influenza vaccination significantly protected against acute myocardial infarction (OR 0.55 95%CI 0.35-0.85) and the authors suggest that failure to vaccinate individual may be a missed opportunity to prevent ischemic heart disease related to influenza [[[3]](#endnote-3)]. Another study reported that among 13,211 patients with coronary artery disease, 24% received aspirin, β-blocker, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and lipid lowering therapy [[[4]](#endnote-4)]. Furthermore, the patients who had a non-ACS event in the 6 months prior did not affect the adjusted proportion on preventative medications and the authors suggest that there may be an opportunity to improve care if clinicians managing non-ACS admissions would consider starting evidence based therapies to target cardiovascular risk factors.

*Diagnosis related missed opportunities*

From the community setting, Zapka et al conducted a random-digit dialed telephone survey of 1293 patients from 20 communities located in 10 states in the United States [[[5]](#endnote-5)]. They found that people who would wait until they were very sure symptoms were heart attack were more likely to be older, reported their insurance did not pay for ambulance services and reported less confidence in known the signs and symptoms themselves while African-Americans and people with more than high school education, reported intentions to act quickly. No measure of personal health history or interaction with primary care physicians or cardiologist were significantly related to ‘acting fast’. This study highlights missed opportunities for healthcare providers and public health/policy makers to educate and encourage patients about their risk and appropriate action.

Missed opportunities have been reported for patients from the primary care perspective. Sequist et al conducted a case control study of patients with missed opportunities defined by outpatient evaluation by primary care clinicians for chest pain or anginal equivalents within 30 days of hospitalization for acute myocardial infarction [[[6]](#endnote-6)]. They found that 27.0% of 966 acute myocardial infarction cases had an office visit in the preceding 30 days and 11.0% did not have referral for hospital care. Patients with a Framingham risk score of 10% or greater were associated with missed opportunities (OR 19.5 95%CI 9.3-40.6) and the authors conclude this score may help identify missed opportunities that warrant more intensive evaluation. Turkay et al evaluated 850 patients with age 30 years or older with no known history of coronary heart disease who were under the care of primary care center in Turkey [[[7]](#endnote-7)]. They found that 14.8% had formerly undiagnosed coronary heart disease based on the Rose questionnaire, physical examination and electrocardiogram and the proportion of patients with hypertension, diabetes, hypercholesterolemia, obesity and current smokers were present in 30.4%, 8.2%, 43.4%, 37.1% and 26.1% respectively.

A few studies considered healthcare contact in hospital prior to onset of serious CAD. The EPIHeart cohort study evaluated patients with first episode of ACS who had preceding chest pain and previous sought medical care and undergone evaluation [[[8]](#endnote-8)]. For the 690 patients with first episode of ACS, preceding chest pain was reported in 61% of patients and 43% sought medical help. Patients who sought help were more likely to be hypertensives (OR 2.13 95%CI 1.29-3.51) and those who were less likely to seek help were former smokers (OR 0.52 95%CI 0.28-0.99) and of higher social class (OR 0.16 95%CI 0.05-0.48). The authors suggest that there are missed opportunities to improve the diagnosis of myocardial ischemia before acute coronary events. Moy et al conduced an evaluation of 111,973 adults in the Healthcare Cost and Utilization Project State Inpatient Databases and State Emergency Department Databases for 2007 [[[9]](#endnote-9)]. They found that 993/112,000 patients had missed diagnoses of acute myocardial infarction (AMI) in the emergency department and were admitted for AMI within 7 days. The patients at highest risk were young and of black race while those from teaching hospitals, hospitals with cardiac catheterization laboratories, high emergency department admission rates, high inpatient occupancy rates and urban locations had lower odds of missed diagnoses. Lang et al reviewed the administrative data for unplanned ACS admission between 2010 and 2012 in Alberta in order to understand missed opportunities to diagnose ACS [[[10]](#endnote-10)]. From 18,216 episodes for care, 7.25% presented to the emergency department 7 days prior to diagnosis for with ACS from reasons including throat and chest pain (23.5%), angina pectoris (9.1%), chronic obstructive pulmonary disease (3.2%) and abdominal pain (3.0%).

*Missed opportunities in acute treatment*

Missed opportunities related to acute treatment is described in several studies. An analysis of 3197 patients in the Gulf RACE registry with STEMI found that delayed presentation and missed reperfusion occurred in 29.1% and 9.3%, respectively [[[11]](#endnote-11)]. Delayed presentation was associated with older age, atypical symptoms and no family history of coronary artery disease while missed reperfusion was associated with older age, prior stroke and atypical symptoms. Tricomi et al evaluated a cohort of 460 patients with STEMI in 5 emergency departments in the United States between 2000 and 2002 and found that 22% did not receive reperfusion therapy. Factors associated with failure to receive reperfusion included old age, peripheral vascular disease and absence of chest pain. Patients seen by both resident and attending physicians were more likely to receive treatment [[[12]](#endnote-12)]. In cases where reperfusion was not performed STEMI was not identified in 34%, left bundle branch block was not considered an indication 13% and there was a reason for withholding guidelines supported therapies 34% and no documented reason for withholding reperfusion in 19%. El Gaylani conducted a study of 2439 patients with acute myocardial infarction and found that 48% failed to receive thrombolytic therapy because of absence of diagnostic electrocardiogram (29.2%), late presentation (5.2%), therapeutic error (4.6%) and bleeding risk (5.7%) [[[13]](#endnote-13)]. Furthermore 5.7% in whom bleeding risk was reported as contraindicated actually could have received thrombolytic therapy and 3.1% would have been suitable for primary PCI that did not receive it.

Simms et al conducted an analysis of 112,286 patients with STEMI who were discharged from hospital alive between 2007 and 2010 from the Myocardial Ischaemia National Audit Project and derived a cumulative missed opportunities for care score based on nine care components (pre-hospital ECG, acute use of aspirin, timely reperfusion, prescription at hospital discharge of aspirin, thienopyridine inhibitor, ACE-inhibitor or equivalent, HMG-CoA reductase inhibitor and β-blocker, and referral for cardiac rehabilitation) [[[14]](#endnote-14)]. Of the eligible patients for all nine components 50% had one or more missed opportunity and patients with no missed care compared to four or missed opportunities had significantly lower mortality at 30-days (0.5% vs 5.4%, adjusted OR per unit increase OR 1.22 95%CI 1.05-1.42).

*Missed opportunities in secondary prevention*

Many studies focus on secondary prevention opportunities for patients with acute myocardial infarction. Shah et al evaluated the data from the National Health and Nutrition Examination Surveys 1999 to 2012 for patients with self-reported history of myocardial infarction and found that temporal trends suggest that there are improvements in cholesterol treatments (from above 80% in 2011-2012 to projected rates of 100% by 2020) but there were still missed opportunities in terms of blood pressure control and the use of aspirin [[[15]](#endnote-15)]. A study of 100 patients with elective angiography or PCI found that there were missed opportunities for secondary prevention [[[16]](#endnote-16)]. β-blockers were used in 71% of patients but only 25% had dosages that were effective from clinical trials and similarly for angiotensin converting enzyme inhibitors treatment and evidence base doses was present in 61% and 83% respectively. Statins were used in 52% of patients and 95% had dosages that were evidence-based. The authors suggest that modern cardiology is quick to embrace technology but fail to control risk factors with evidence-based therapies. Data from the APTOR study taking place in 14 European countries between 2007 to 2009 found that optimal therapy was received in 43% of patients, with diet, regular exercise and dual antiplatelet therapy being particularly low [[[17]](#endnote-17)]. The authors suggest that there may be a missed opportunity to improve patient outcomes with better adherence to guideline-based therapy provided that there were not appropriate decision to deviate from guidelines. A cross sectional study of missed opportunities for secondary prevention of coronary heart disease in low and middle income countries found that 82%, 89% and 77% of patients were aware of the benefits for quitting smoking, a heart-healthy diet and regular exercise, respectively [[[18]](#endnote-18)]. Only 52.5% engaged in less than 30 min of physical exercise a day, 35% did not follow a heart healthy diet and 12.5% were current tobacco users. The use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors and statins was 81.2%, 48.1%, 39.8% and 29.8%, respectively and only about 1 in 5 had revascularization.

*Missed opportunities related to statin therapy*

 Statins are lipid lowering drugs with proven effectiveness in CAD so there has been particular interest use of these agents in the secondary prevention after AMI. One study evaluated statin discontinuation at 182 days post discharge for Medicare beneficiaries with a statin pharmacy fill claim within 30 days of hospital discharge for a myocardial infarction in 2007 to 2012 [[[19]](#endnote-19)]. They found that re-initiation of statin was associated with lipid panel testing (OR 2.65 95%CI 1.93-3.65), outpatient primary care (OR 1.31 95%CI 1.23-1.40) and outpatient cardiologist care (OR 1.38 95%CI 1.28-1.50) for routing healthcare utilization and for acute healthcare utilization statin re-initiation was associated with emergency department visit (OR 1.77 95%CI 1.31-2.40), coronary heart disease hospitalizations (OR 3.16 95%CI 2.14-4.14) and non-coronary heart disease hospitalization (OR 1.73 95%CI 1.49-2.01). There findings suggest there are missed opportunities to reinforce the importance of statin therapy as secondary prevention in both routine and acute healthcare settings. de Lemos et al found that among 1,750 patients with ACS, 64% had an indication for statin therapy before enrolment and that initiations statin therapy at moderate dosages would have prevent 15% of ACS events and intensive therapy would prevent >21% of events [[[20]](#endnote-20)]. A simulation analysis of 7285 patients with AMI discharged from 102 hospitals between 1999 and 2001 in Ontario Canada found that 35.6% of patients had statin therapy at hospital discharge [[[21]](#endnote-21)]. Estimates of increasing statin prescribing among patients least likely to received treatment could reduce AMI mortality by 83 deaths per year and increasing statin prescribing to 70% of all patients with AMI could avert 312 deaths per year.

*Other missed opportunities in secondary prevention*

An Australian study from the Cooperative National Registry of Acute Coronary Care, Guideline Adherence and Events (CONCORDANCE) and Global Registry of Acute Coronary Events (GRACE) registries found that 532 patients with a history of atrial fibrillation had oral anticoagulant (36%), 580 patients had antiplatelet (39%) and 367 patients had no antithrombotic therapy (39%) [[[22]](#endnote-22)]. During the 18 years of the study, the use of oral anticoagulants increased from 27% to 56%. The authors suggest that the receipt of oral anticoagulation therapy remains suboptimal with minimal escalation in provision of oral anticoagulation therapy during hospital care which represents a missed opportunity.

Data from the NORIN STEMI registry from tertiary medical centers in India reported that there are missed opportunities for screening and management of dysglycemia after myocardial infarction [[[23]](#endnote-23)]. Among the 3,635 patients with STEMI, 24% had a prior history of diabetes mellitus and use of SGLT2 inhibitors and GLP-1 receptor antagonists were low (0.1% and 2%, respectively). The authors conclude that protocolized HbA1c screening doubles the proportion of patients with known dysglycemia and these patients have increased rates of left ventricular dysfunction and mortality at 30 days.

Sollien et al evaluated a nationwide cohort of 49,479 patients with first time myocardial infarction in Denmark and found that 18.4% had an indication for eplerenone but only 1.02% received it and 22.5% had spironolactone [[[24]](#endnote-24)]. The authors estimate that this translated to 164 and 431 deaths could have been saved by guideline-recommended use of eplerenone.

An evaluation of the primary percutaneous coronary intervention program in the Middle East in 2013 to 2014 found that a Zowlle risk score ≤3 compared to >3 was associated with shorter mean length of stay (3.5 vs 7.7 days) [[[25]](#endnote-25)]. However, at least half of the 88% of patients who are eligible for early discharge stay longer than 3 days which reflects a missed opportunity to reduce cost associated with longer length of stay.

Boggon et al evaluated missed opportunities in encouraging smoking cessation for patients with acute coronary syndrome in the Myocardial Ischaemia National Audit Project registry linked to General Practice Research Database, Hospital Episode Statistics and Office of National Statistics mortality data [[[26]](#endnote-26)]. They found that 20% of 4834 patients were smokers at time of acute coronary syndrome. Only 24% received GP smoking intervention within 3 months with 9% receiving advice only and 15% receiving pharmacological intervention. In those who quit smoking (33%) there was reduced risk of mortality (RR 0.49 95%CI 0.34-0.69) and major adverse cardiovascular events (RR 0.61 95%CI 0.46-0.80).

Missed opportunity for taking part in cardiac rehabilitation after myocardial infarction was explored in a qualitative study of 27 people who did not take part in cardiac rehabilitation [[[27]](#endnote-27)]. The study found that factors influencing non-participants were either related to themes of no need/point, not worth it or not possible and there were shifts between categories over time.

**Discussion**

This review highlights the diverse application of the term ‘missed opportunities’ in coronary heart disease. While missed opportunities is a nonspecific term, an approach to its definition can be ‘missed opportunities related to prevention, early identification, diagnosis and management that is specific to the condition and healthcare setting.’ In the context of CAD, primary prevention opportunities highlighted in the literature include the management of patients with risk factors and immunizations. In terms of diagnosis, a proportion of patients who have underlying CAD had a hospital admission where there was a missed opportunity to diagnose the condition before patients represent with more serious disease such as ACS. In the case of ACS where there is need for acute treatment, there are missed opportunities related to delay in diagnosis and missed reperfusion therapy. Finally, after acute treatment, most of the literature looks at missed opportunities for secondary prevention such as smoking cessation, exercise, weight loss, attendance at cardiac rehabilitation and receipt of evidenced based therapies including antihypertensives, antiplatelet and statin therapy. These findings suggest that missed opportunities are present in many aspects of the care of patients with CAD. More studies are needed in order to understand these missed opportunities could be reduced.

Identification of missed opportunities is a data driven process. Health services aim to manage patients safely by minimize harm from delays to investigation and treatment. In some facilities, there are care pathways that have been developed to handle frequent and important conditions. However, the care received by patients is not always optimized. Data collection and evaluation is essential to demonstrate efficiency and cost-effectiveness. It is only through scrutinizing real-world activities in detail and reflecting on the quality of patient care and associated outcomes that can enable suboptimal care to be identified. Central in this is critical appraisal on how things could have been done better. Ideally to understand what is happening, resources and energy need to be invested to have high quality granular data beyond what is captured routinely. This is necessary in order to not only capture untoward events but also explain why it happened so that interventions can be used to prevent them from happening it in the future. For example, a patient may have been prescribed a secondary prevention medication but on their routine records it was noted they stopped taking the medication. This could have been interpreted as a missed opportunity as the patient will not have the same benefit as all the other patients who had the treatment. However, if the patient had an adverse effect, it may be justified that the impact of medication use on the quality of life may override the benefit associated with the medication. This is particularly important consideration as many of the studies collected data from databases that were not designed to understand why medications were not adhere to despite clinical recommendations for therapy.

Missed opportunities should be evaluated by researchers with unbiased expertise in a systematic approach. The evaluator should be familiar with good practice in order to recognize where things could have been improved. It is clear that in the litigious environment of modern medicine that acknowledgement that patients may have experienced harm is something frequently avoided. However, only by reviewing what happens can improvements be made. For example, some studies suggest that healthcare contacts within a certain time from of ACS admission reflects a missed opportunity for early identification. However, the prior healthcare contact before ACS admission must have had clinical features suggestive of ischemic heart disease otherwise it may be unlikely to make the earlier diagnosis and the subsequent admission for ACS may be unavoidable. Furthermore, the investigator needs to be familiar with the healthcare system and healthcare structure. For example, in a private healthcare system suboptimal care such as lack of treatment may relate to lack of financial ability to pay for treatment which is a missed opportunity but not really avoidable. Similarly, there may be logistic constraints such as patients living in rural areas with limited access to specialist opinions and tests. These factors may not be always be captured in medical insurance databases which are not designed to capture these variables. Finally, a systematic approach should be used to better identify all potential opportunities. Opportunities should be considered when the patient is in the community in the absence of healthcare contact and when they contact healthcare professionals such as primary care, secondary care and community care. An alternative approach may be from a patient perspective considering exactly how they arrived at their current point in their care by retrospectively consider all healthcare contacts. These sorts of approaches minimizes the potential for missing data that might help rationalize real-world clinical events.

The care of patients with CAD can be divided into pre-healthcare professional contact, at time of acute illness and post treatment secondary prevention period. With today’s evidence and guideline-based practice, the standard of care for symptoms of angina and ACS is effective with many antianginals, power antiplatelet drugs, coronary revascularization and secondary prevention measures. It is arguable that once a patient sees a specialist most of them will receive decent quality care. Therefore, the major gains from missed opportunities relates to early diagnosis, early administration of statins, lifestyle modifications, cardiac/exercise rehabilitation and ensuring appropriate patients see specialists within a time frame. This is particularly important in the context of delayed presentation to specialist which can have serious consequences particularly with ACS causing cardiac arrest and irreversible heart failure. This highlights the role of public education and health promotion campaigns to encourage patients to seek help and other strategies to encourage public not to ignore their symptoms.

The issue of missed opportunities related to primary prevention of coronary artery disease is not straight forward. Almost every adult is at risk of atherosclerosis and coronary artery disease but it is not clear what timepoint in their life patients should be screened. Screening with imaging such as calcium score or computed tomography coronary angiography can help identify patients and increase adherence to statins. While every patient may benefit from this form of evaluation at some point in their life, whether it is practical to implement such testing depends on the population and healthcare system.

It is important that missed opportunities extend beyond care outcomes but also to the delivery of cost-effective care. While treating patients may reduce their likelihood of adverse outcomes, this has to be balanced against the cost of early identification and treatment. This is particularly important in public healthcare systems like the National Health Service in the United Kingdom where there are only limited resources and any mechanism to reduce cost while ensure the same quality of care should be promoted. This is very different from private healthcare systems where patients may choose to invest more of their personal funds to pay for additional care beyond the minimum standard. However, this creates heterogeneity and complexity in care which contributes to patients having different levels of care and thus a variable number of missed opportunities.

An area for future work is understanding how closing the opportunity gap would impact mortality. An issue related to missed opportunities is that the effect of avoiding the missed opportunity will depend on the exact opportunity. For instance, prevention and screening may have two major impacts. First, it could stop the onset of disease but secondly, it could shift the onset of disease to a later time. This may reduce mortality related to coronary heart disease but these patients may instead develop other conditions such as cancer which may result in mortality. Earlier diagnosis and a reduction in missed opportunities related to delay and misdiagnosis could have different positive effects on mortality depending on the type of coronary heart disease. For patients with stable angina, identification of patients with this condition places patients at lower risk of mortality compared those who then present with acute coronary syndrome. For patients with acute coronary syndrome, early diagnosis would yield greater mortality benefit for revascularization. A reduction in missed opportunities for treatment should reduce mortality. As most evidence-based therapies are used because of their benefit in terms of mortality or complications which would have downstream impacts on risk of mortality.

Missed opportunities are good starting points for clinical audits and service evaluations. Setting standard that patients should receive evidence-based treatments and then auditing them could provide evidence to substantiate suspicions that care could be improved. From the audit findings, an intervention could be introduced to increase the patients meeting the standards and closing the loop of the audit will demonstrate how the intervention has affected clinical practice. Through this iterative cycle it is possible to improve care by minimizing missed opportunities.

**Conclusions**

Missed opportunities can become apparent if looked for in care of patients with CAD. While the term is non-specific, it should be contextualized in opportunities related to prevention, diagnosis and treatment. Only through reflection on clinical activities in relation to patient outcomes and the healthcare service can missed opportunities be identified so that better care can be delivered.

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