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Canadian Journal of Diabetesjournal homepage:
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CANADA**

2018 Clinical Practice Guidelines

Management of Acute Coronary Syndromes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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**KEY MESSAGES**

- Over the past 20 years, the rates of acute myocardial infarction in people with diabetes has decreased substantially. However, the burden of disease remains high because of the increased prevalence of diabetes.
- Diabetes and hyperglycemia are independent predictors of increased short- and long-term mortality, recurrent myocardial infarction, and the development of heart failure in patients with acute myocardial infarction.
- People with an acute myocardial infarction and hyperglycemia (random blood glucose >11.0 mmol/L) may receive antihyperglycemic therapy to maintain blood glucose levels between 7.0 to 10.0 mmol/L.
- People with diabetes are less likely to receive recommended treatment, such as an early invasive strategy and revascularization, reperfusion therapy, beta blockers or dual antiplatelet therapy than people without diabetes. Efforts should be directed at promoting adherence to existing proven therapies in the high-risk person with myocardial infarction and diabetes.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- A heart attack can manifest as chest discomfort or crushing pain; or as pain in the arms, back, neck, jaw and, even, the stomach. Shortness of breath, cold sweat, nausea and lightheadedness may also occur.
- If you are experiencing symptoms of a heart attack, you should seek medical help immediately. The faster treatment is started, the better.

Introduction

Diabetes (together with lipid abnormalities, smoking and hypertension) is one of the top 4 independent risk factors for myocardial infarction (MI) (1). Today, approximately 15% to 35% of people admitted with an acute coronary syndrome (ACS) have known diabetes (2), and as many as a further 15% have undiagnosed diabetes (3). Between 1990 and 2010, there was a 67.8% reduction of the rates of acute MI in people with diabetes, compared to a 32% reduction in individuals without diabetes (4). However, as a result of the substantial increase in the prevalence of diabetes over this period, the public health burden of MI in people with diabetes continues to rise.

Compared to individuals without diabetes, people with diabetes have:

- A 3-fold increased risk of ACS (5)
- Occurrence of acute coronary events 15 years earlier (5)
- A 2-fold increased short- (6,7) and long-term mortality (6,8)

Conflict of interest statements can be found on page S193.

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<https://doi.org/10.1016/j.jcjd.2017.10.029>

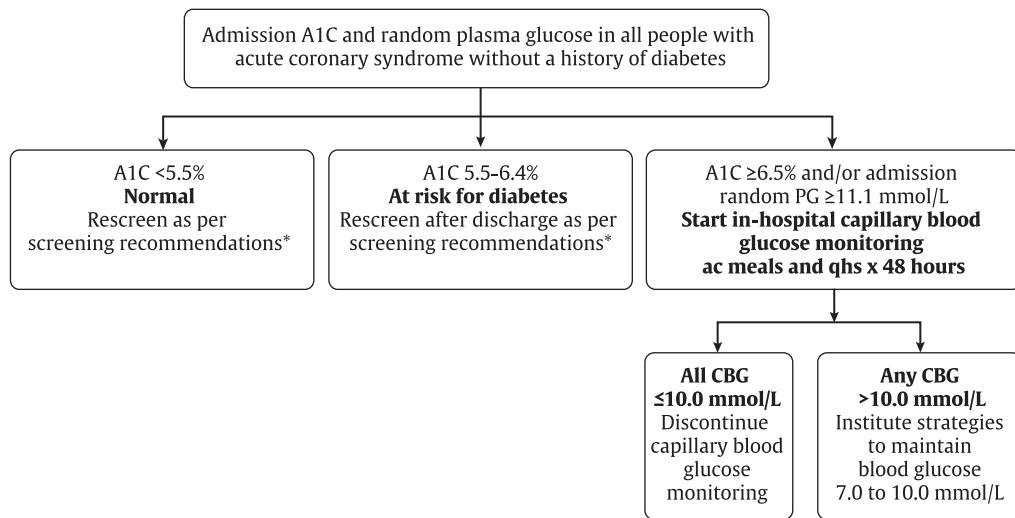
- An increased incidence of post-infarction recurrent ischemic events, heart failure and cardiogenic shock (3,9)
- A similar benefit from guideline-recommended management strategies (see below)
- Less utilization of guideline recommended care (10–13), including an invasive strategy (14) which may contribute to adverse outcomes (15).

Risk Stratification of People With Diabetes and ACS

It is recognized that there is a wide range of risk for an adverse outcome in people with diabetes after an ACS. A recent study developed a prediction model that indicated age, renal dysfunction, the presence of anemia, heart failure or left ventricular (LV) dysfunction, in-hospital revascularization, obesity, prior ACS and insulin treatment were factors significantly associated with mortality during the 5 years after acute MI (AMI) (16).

Identification of Diabetes in People with ACS

Although the absolute number of people with MI has fallen in the United States, the prevalence of diabetes in this population has steadily increased from 18% in 1997 to 30% in 2006 (16). More than two-thirds of people with MI have either diabetes or prediabetes (impaired glucose tolerance [IGT] or impaired fasting glucose [IFG]) (17). Abnormal glucose regulation is almost twice as prevalent in people with MI compared to a matched control population and is a marker for adverse outcomes (18). The frequency of previously unrecognized diabetes in the ACS population is reported to be between 4% and 22% depending on the test used for the diagnosis of diabetes (3,19). If fasting plasma glucose (FPG) criteria is used alone in the ACS population, diabetes is underdiagnosed in 39% compared to when the diagnosis is made from an oral glucose tolerance test (OGTT) (20). An A1C >6.5% is currently a diagnostic criterion for diabetes as it captures long-term glucose exposure, does not require fasting or timed samples and is currently used to guide management decisions (see Screening for Diabetes in Adults chapter, p. S16). One study has validated the use of A1C in an acute care population and found that using the 2-hour 75 g OGTT as a gold standard for the diagnosis of diabetes, and an A1C threshold of 6.0%, A1C had a sensitivity of 77% and a specificity of 87% (21). It is accepted that some people with diabetes will be missed by screening with fasting plasma glucose (FPG) and A1C compared to the universal use of an OGTT. However, it is likely that the people most in



ACS, acute coronary syndrome; BG, blood glucose; CBG, capillary blood glucose monitoring; PG, plasma glucose.

*See Figure 1. Screening for Diabetes in Adults chapter, p.S16.

Figure 1. Screening for type 2 diabetes in people with ACS.

need of glycemic control will be detected with these simple tests that can be widely applied. In-hospital capillary blood glucose monitoring should be started in individuals without a history of diabetes with an admission A1C $\geq 6.5\%$ or random plasma glucose (PG) $> 10.0 \text{ mmol/L}$. Individuals with an A1C between 5.5% to 6.4% should have repeat screening after discharge as per diabetes screening guidelines (see Screening for Diabetes in Adults chapter, p. S16 and Figure 1).

Management of ACS in People With Diabetes

Guidelines for the management of people with ACS have been developed by the American College of Cardiology/American Heart Association (22–24) and the European Society of Cardiology (25,26). In most situations, there are no clinical trials that specifically address management of people with diabetes and ACS; however, subgroup analyses in people with diabetes and ACS show either a similar or enhanced benefit from treatment compared to the overall group for: a) reperfusion with fibrinolysis (27) or primary angioplasty (28) for ST-segment elevation ACS; and b) an early invasive strategy (29) with the use of dual anti-platelet therapy with acetylsalicylic acid (ASA) and clopidogrel (30), glycoprotein IIb/IIIa inhibitors and the newer P2Y12 platelet inhibitors (prasugrel and ticagrelor) in people with non-ST segment elevation ACS at high risk of recurrent ischemic events (31).

A significant care gap exists for people with diabetes not receiving guideline-recommended treatment compared to people without diabetes (10–12,15,16). It is possible that the underutilization of recommended treatment is one factor contributing to the adverse outcome of the person with diabetes and ACS.

Anti-Platelet Therapy and ACS in People With Diabetes

Platelet aggregation plays a central role in the development of the occlusive thrombus responsible for acute coronary occlusion in people with ACS. People with diabetes have a pro-thrombotic state due to dysfunctional and hyperactive platelets, endothelial dysfunction, elevated coagulation factors and decreased fibrinolysis (32). Increased platelet activity is due to multiple metabolic and cellular

factors associated with diabetes that include endothelial dysfunction, the impact of hyperglycemia and deficient insulin action (32).

Diabetes is associated with an increased incidence of recurrent atherothrombotic events (33), including stent thrombosis (34). Anti-platelet therapy has been shown to reduce atherothrombotic events in people with ACS, both during the acute phase and in the longer term. The beneficial effect of ASA has been shown in multiple clinical trials in patients with non-ST-segment elevation acute coronary syndrome (NSTE ACS) and ST-segment elevation MI (STEMI). The Antithrombotic Trialist's Collaboration meta-analysis (35) of anti-platelet therapy (mainly ASA) included 212,000 high-risk participants (with acute or previous vascular disease) and showed the incidence of vascular events to be reduced in both the overall population (16.8% to 12.8%; $p<0.00001$) and in the participants with diabetes (22.3% to 18.5%; $p<0.002$). Low-dose ASA (75 to 150 mg) was as effective as higher doses ($>150 \text{ mg}$) with a lower incidence of bleeding complications. The Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-Organization to Assess Strategies in Ischemic Syndromes (CURRENT/OASIS 7) trial (36) also was unable to show any benefit from higher dose compared to low-dose (75 to 100 mg) ASA in people with and without diabetes. The use of low-dose ASA is recommended to minimize GI bleeding in people with and without diabetes (see Cardiovascular Protection in People with Diabetes chapter, p. S162).

Dual anti-platelet therapy with ASA and clopidogrel, administered from the time of presentation, has been the recommended standard of care for people with NSTE ACS. People with diabetes in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (30) had a similar benefit with clopidogrel vs. placebo (14.2% vs. 17.7%, RR 0.84, 95% CI 0.70–1.02) as the overall population (9.3% vs. 11.4%, RR 0.80, 95% CI 0.72–0.90). Despite dual-antiplatelet therapy with ASA and clopidogrel, recurrent atherothrombotic events continue to occur, especially in the person with diabetes. Clopidogrel is a relatively weak inhibitor of platelet aggregation with a wide variation of inhibition of in-vitro platelet aggregation. There is a higher incidence of events in people with residual platelet activity and people with diabetes have higher residual platelet activity despite ASA and clopidogrel treatment. Two more potent antiplatelet agents, prasugrel and ticagrelor, that are more effective and predictable inhibitors of platelet aggregation, have been shown to improve outcomes, especially in people with diabetes.

In the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel - Thrombolysis In Myocardial Infarction (TRITON-TIMI 38) trial, prasugrel administered at the time of coronary angioplasty in participants with ACS reduced recurrent ischemic events, including stent thrombosis, compared to participants receiving clopidogrel (37). In subjects with diabetes, prasugrel treatment was associated with greater platelet inhibition and fewer poor responders (38). Prasugrel resulted in an important net clinical benefit in people with diabetes (39) (14.6 vs. 19.2%, HR 0.74, p=0.001) due to a 30% reduction of the primary endpoint (cardiovascular [CV]) death, non-fatal MI or stroke over the 14.4 months of the study. In this subgroup with diabetes, there was no significant increase in major bleeding. There was no statistical interaction between the subgroups with and without diabetes, indicating that the enhanced absolute benefit was the result of higher event rates in people with diabetes.

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, the P2Y₁₂ receptor antagonist ticagrelor, when compared with clopidogrel and administered early after presentation in people with NSTE ACS or STEMI, reduced CV death, non-fatal MI and stroke (10.2% vs. 12.3%, HR 0.84, p=0.0001), as well as CV death (4.0% vs. 5.1%, HR 0.49, p=0.001) and stent thrombosis (2.2% vs. 2.9%, HR 0.75, p=0.02) with a modest increase in bleeding in people not undergoing coronary bypass surgery (40). In the diabetic cohort of the PLATO study, similar benefits were observed as in the overall group (41).

The availability of more potent and reliable anti-platelet agents for the management of people with ACS provides an opportunity to further reduce recurrent ACS and mortality. High-risk people with diabetes with either STEMI or NSTE ACS should be considered for treatment with either prasugrel (after the coronary disease anatomy has been defined) or ticagrelor.

Platelet aggregation is largely mediated by the glycoprotein (GP) IIb/IIIa receptor through its binding to fibrinogen. The GPIIb/IIIa receptor inhibitors abciximab, eptifibatide and tirofiban were shown to be effective for the management of ACS in people with diabetes in a meta-analysis of 6 clinical trials. GPIIb/IIIa inhibitors were shown to reduce 30-day mortality by 26% (4.6% vs. 2.6%, p=0.007) (31). In contrast, people without diabetes had no mortality benefit. Although these trials were performed in an era before dual anti-platelet therapy with ASA and clopidogrel was used, studies (42,43) indicate an additional benefit from a GPIIb/IIIa inhibitor for people with high-risk ACS, such as those with diabetes who are undergoing percutaneous coronary intervention (PCI). However, these benefits have not been observed when more potent oral anti-platelet agents, such as ticagrelor, are used (44).

More prolonged duration dual anti-platelet therapy with ASA and ticagrelor in people with ACS, administered for up to 3 years beyond the usual 1-year treatment, was shown in the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial to reduce the primary endpoint of non-fatal MI, stroke or CV death (placebo 9.04% ticagrelor 60 mg 7.77% (hazard ratio [HR] 0.84, 95% CI 0.74–0.95), ticagrelor 90 mg 7.85% (HR 0.85, 95% CI 0.75–0.96) (44). There was no advantage to receiving ticagrelor 90 mg twice daily rather than 60 mg twice daily, and major bleeding was slightly more at the higher dose (placebo 1.06%, ticagrelor 60 mg 2.3%, ticagrelor 90 mg 2.6%). Participants with diabetes receiving ticagrelor, had a similar relative risk reduction of the primary combined endpoint as the overall group (45). However, with a 50% higher event rate, those with diabetes had an 60% greater absolute benefit than the participants without diabetes (participants with diabetes: placebo 11.6%, ticagrelor 60 mg twice daily 10.0% [HR 0.83, 95% CI 0.69–1.00]; participants without diabetes: placebo 7.8%, ticagrelor 6.7% [HR 0.84, 95% CI 0.72–0.98]). The increased bleeding rates with ticagrelor were similar in the people with diabetes to those without

diabetes. People at very high risk or recurrent ischemic events (such as people with extensive coronary artery disease [CAD] not completely revascularized, or recurrent ACS despite usual recommended treatment) and with a low or average bleeding risk, should be considered for prolonged (up to 3 years post-ACS) treatment with ticagrelor 60 mg twice daily.

Glycemic Control

Hyperglycemia during the first 24 to 48 hours after admission for ACS is associated with an increased early mortality, whether or not the person has diabetes (46,47). Furthermore, in-hospital mortality has a closer relationship to hyperglycemia than to diabetic status (48,49). Higher baseline blood glucose (BG) and a failure of BG to decrease are independent predictors of mortality (50). For people undergoing primary angioplasty, mortality increases when the plasma glucose (PG) is >10.0 mmol/L (47).

Although elevated mean BG level in the first 24 hours after onset of ACS is associated with adverse outcomes (51), evidence to support reducing BG levels (especially to levels close to the normal range) after ACS, remains inconclusive. The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) study indicated that tight glycemic control with the use of intravenous insulin in the early hours after presentation, followed by multidose subcutaneous insulin treatment over the subsequent months, resulted in a 30% reduction in 1-year mortality (52–56). The DIGAMI 2 study failed to achieve the study goals, both in the number of participants recruited and in glycemic targets (52). However, despite these limitations, it did demonstrate that outcomes were closely related to glycemic control, however achieved. Studies have shown that glucose-insulin-potassium infusion in patients with AMI do not improve outcomes; however, these protocols often resulted in increased BG levels and, therefore, cannot be used as evidence for outcomes associated with glycemic control. In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study of glucose and insulin in people with AMI, participants with a blood glucose maintained at <8.0 mmol/L had lower mortality than subjects with higher levels (57).

In conclusion, clinical trial data do not conclusively show that tight glycemic control early after an ACS improves long-term outcomes. Furthermore, the impact of hypoglycemia may negate any potential benefit. Glycemic control in the post MI patient should be consistent with the Diabetes Canada clinical practice guidelines recommendations for management of hyperglycemia in the hospitalized patient (see In-Hospital Management of Diabetes chapter, p. S115).

Revascularization

ACS practice guidelines promote the same treatment strategies in people with diabetes as for those without diabetes (58). An early invasive strategy with revascularization when possible in non-ST elevation (NSTE) ACS provides a similar or greater reduction in death and MI (up to 5 years of follow up) in the subset of participants with diabetes compared to the overall population (27,59,60). An early invasive, rather than a selective invasive (conservative), strategy is recommended, in the absence of contraindications in people with diabetes and a NSTE ACS.

Trials comparing coronary artery bypass grafting (CABG) and PCI in people with diabetes with stable multivessel disease or ACS have provided consistent results in favour of CABG (61) with improved outcomes of death, MI and repeat revascularization, despite an excess of stroke in people undergoing CABG. These results are generally extrapolated to the higher-risk ACS population with diabetes with

NSTE-ACS and complex coronary anatomies. Therefore, CABG with the use of internal thoracic artery bypass should be the preferred revascularization modality over complex PCI in light of the consistent results in randomized trials with the provision that patient characteristics (such as frailty, cerebrovascular disease, among others) need to be considered. Percutaneous coronary interventions (with newer generation drug-eluting stents whenever possible) is acceptable for people with less extensive disease (i.e. single-vessel disease or 2-vessel disease without involvement of the left anterior descending (LAD) and those with Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score ≤22) (62).

For people with ST-elevation ACS, immediate reperfusion strategies with either fibrinolysis or primary PCI (PPCI) result in similar benefits for people with and without diabetes. The benefits of PPCI over fibrinolysis in people with diabetes are similar to those in the population without diabetes (Odds ratio [OR] mortality with primary PCI vs. fibrinolysis in people with diabetes 0.49 [95% CI 0.31–0.79]) (27). However, fibrinolysis should be administered when PPCI is not available, within acceptable timeframes. Ocular hemorrhage in people with diabetic retinopathy is extremely rare and should not limit the use of fibrinolysis when it is indicated (59).

RECOMMENDATIONS

1. In all people with ACS, a random BG and an A1C (if not done in the 3 months prior to admission) should be measured:
 - a. For people with a history of diabetes, to identify individuals that would benefit from glycemic optimization [Grade D, Consensus]
 - b. For people without a history of diabetes, to identify individuals at risk for ongoing dysglycemia [Grade D, Consensus]
 - i. If the A1C is ≥6.5% and/or random BG is >11.0 mmol/L, in-hospital capillary blood glucose monitoring should be initiated [Grade D, Consensus]
 - ii. If A1C is 5.5–6.4%, repeat screening for diabetes should be performed after discharge as per diabetes screening recommendations [Grade D, Consensus] (see Figure 1. Screening for Diabetes in Adults chapter, p. S16).
2. In-hospital management of diabetes in ACS should include strategies to avoid both hyperglycemia and hypoglycemia:
 - a. People with ACS and a random BG of >11.0 mmol/L on admission may be treated to achieve BG levels in the range of 7.0–10.0 mmol/L followed by strategies to achieve recommended BG targets long term [Grade C, Level 2 (52,55)]. Insulin therapy may be required to achieve these targets [Grade D, Consensus]
 - b. An appropriate protocol should be developed and staff trained to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia [Grade D, Consensus].
3. People with diabetes and ACS should receive the same treatments that are recommended for people with ACS without diabetes since they benefit equally [Grade D, Consensus].
 - a. In people with diabetes and ACS undergoing PCI, antiplatelet therapy with prasugrel (if clopidogrel naïve, <75 years of age, weight >60 kg, and no history of stroke) [Grade A, Level 1 (37,39)] or ticagrelor [Grade B, Level 1 (40,41)], rather than clopidogrel, should be used to further reduce recurrent ischemic events. People with diabetes and non-ST-E ACS and higher risk features destined for a selective invasive strategy should receive ticagrelor, rather than clopidogrel [Grade B, Level 2 (40,41)]
 - b. In people with diabetes and ACS, at very high risk of recurrent ischemic events and at average or low bleeding risk, prolonged (up to 3 years post ACS) treatment with ticagrelor 60 mg twice daily should be considered [Grade B, Level 2 (45)]
 - c. In people with diabetes and non-ST-E ACS and high risk features, an early invasive approach, rather than a selective invasive approach to revascularization, should be used to reduce recurrent coronary events, unless contraindicated [Grade B, Level 2 (29)]
 - d. For people with diabetes with NSTE-ACS and complex coronary anatomy, CABG should be considered rather than complex PCI [Grade A, Level 1 (62)]

- e. In people with diabetes and STE-ACS, the selection of the reperfusion modality (PPCI vs. fibrinolysis) should not differ from people with STE-ACS without diabetes; the presence of retinopathy should not be a contraindication to fibrinolysis [Grade B, Level 2 (59)].

Abbreviations:

A1C, glycated hemoglobin; ACS, acute coronary syndrome; AMI, acute myocardial infarction; ASA, acetylsalicylic acid; BG, blood glucose; CABG, coronary artery bypass grafting; CI, confidence interval; CV, cardiovascular; FPG, fasting plasma glucose; HR, hazard ratio; IGT, impaired glucose tolerance; LV, left ventricular; MI, myocardial infarction; NSTE, non-ST-elevation; OGTT, oral glucose tolerance test; OR, odds ratio; PPCI, percutaneous coronary intervention; PG, plasma glucose; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Other Relevant Guidelines

In-Hospital Management of Diabetes, p. S115.

Author Disclosures

Dr. L.-L'Allier reports minor personal fees from Philips (Volcano) and Abbott-SJM, while contributing to the guidelines. Dr. Fitchett reports personal fees from AstraZeneca, Sanofi, and Lilly.

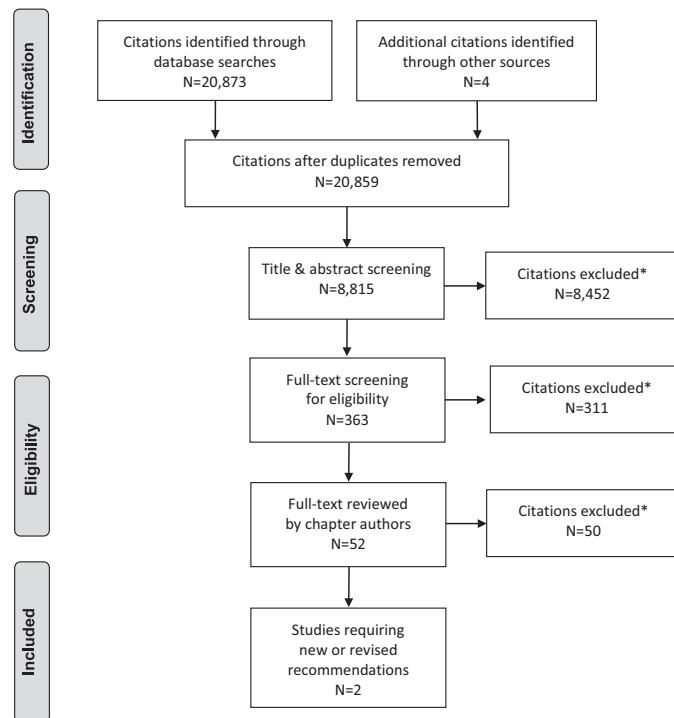
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Literature Review Flow Diagram for Chapter 27: Management of Acute Coronary Syndromes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed.1000097 (63).

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