Canadian Journal of Cardiology 35 (2019) 821–830

Clinical Research

Acute Myocardial Infarction in Severe Mental Illness: Prevalence, Clinical Outcomes, and Process of Care in U.S. Hospitalizations

Mohamed Osama Mohamed, MB BCh, MRCP(UK),[a] Muhammad Rashid, MBBS, MRCP(UK),[a] Saeed Farooq, PhD, FCPS(Psych),[b,c] Nishat Siddiqui, MB BCh, MRCP(UK),[d] Purvi Parwani, MD,[e] David Shiers, MB ChB, MRCP(UK), MRCGP,[f] Ritu Thamman, MD,[g] Martha Gulati, MD,[h] Ahmad Shoaib, MD,[a] Carolyn Chew-Graham, BSc, MB ChB, MD, FRCGP,[b,c] and Mamas A. Mamas, MA, MRCP, DPhil[a]

[a] *Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute of Applied Clinical Science and Primary Care and Health Sciences, Keele University, Keele, United Kingdom*

[b] *Research Institute for Primary Care and Health Sciences, Keele University, Keele, United Kingdom*

[c] *Midlands Partnership NHS Foundation Trust, Staffordshire, United Kingdom*

[d] *Nevill Hall Hospital, Aneurin Bevan University Health Board, Wales, United Kingdom*

[e] *Division of Cardiology, Department of Medicine, Loma Linda University Health, Loma Linda, California, USA*

[f] *Psychosis Research Unit, Greater Manchester Mental Health NHS Foundation Trust, Manchester, United Kingdom*

[g] *Department of Cardiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA*

[h] *Division of Cardiology, University of Arizona, Phoenix, Arizona, USA*

See editorial by Kaur and Schulman-Marcus, pages 797-798 of this issue.

ABSTRACT

Background: Severe mental illness (SMI) is associated with increased cardiovascular mortality. We sought to examine the prevalence, clinical outcomes, and management strategy of patients with SMI presenting with acute myocardial infarction (AMI).

Methods: All AMI hospitalizations from the National Inpatient Sample were included, stratified by mental health status into 5 groups: no SMI, schizophrenia, other non-organic psychoses (ONOP), bipolar disorder, and major depression. Regression analyses were performed to assess the association (adjusted odds ratios [ORs], $P \leq 0.001$ for all outcomes) between SMI subtypes and clinical outcomes.

RÉSUMÉ

Contexte : Le trouble mental grave (TMG) est associé à une augmentation de la mortalité cardiovasculaire. Nous avons étudié la prévalence des patients atteints d'un TMG qui avaient subi un infarctus aigu du myocarde (IAM) ainsi que les résultats cliniques et les stratégies de prise en charge chez ces patients.

Méthodologie : Toutes les hospitalisations pour un IAM répertoriées dans la base de données National Inpatient Sample ont été incluses et stratifiées en 5 groupes selon l'état de santé mentale du patient : absence de TMG, schizophrénie, autres troubles psychotiques non organiques (ATPNO), trouble bipolaire et dépression majeure. Des

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with severe mental illness (SMI), including schizophrenia, bipolar disorder major depression, and psychosis and delusional disorders.[1-4] It is estimated that more than 10.4 million adults (4.2% of all adults) have SMI in the United States, with a similar worldwide prevalence of up to 6.8%.[5,6]

Patients with SMI are reported to have a 2- to 3-fold increased risk of mortality from cardiovascular disorders compared with the general population, a risk that has increased over the past 2 decades.[7] Acute myocardial infarction (AMI) is the most common manifestation of CVD, but there is limited literature on the prevalence, treatment strategies, and clinical outcomes of patients with SMI who are

Received for publication March 24, 2019. Accepted April 25, 2019.

Corresponding author: Prof Mamas A. Mamas, Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, Keele ST5 5BG, United Kingdom. Tel.: +44 (0)1782 733902; fax: +44 (0)1782 73390.

E-mail: mamasmamas1@yahoo.co.uk

See page 829 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.04.021

Results: Of 6,968,777 AMI hospitalizations between 2004 and 2014, 439,544 patients (6.5%) had an SMI diagnosis. Although patients with schizophrenia and ONOP experienced higher crude rates of in-hospital mortality and stroke compared with those without SMI, only schizophrenic patients were at increased odds of mortality (OR, 1.10; 95% confidence interval [CI], 1.04-1.16), whereas ONOP was the only group at increased odds of stroke (OR, 1.53; 95% CI, 1.42-1.65) after multivariate adjustment. Patients with ONOP were the only group associated with increased odds of in-hospital bleeding compared with those without SMI (OR, 1.11; 95% CI, 1.04-1.17). All those with SMI subtypes were less likely to receive coronary angiography and percutaneous coronary intervention, with the schizophrenia group being at least odds of either procedure (OR, 0.46; 95% CI, 0.45-0.48 and OR, 0.57; 95% CI, 0.55-0.59, respectively).

Conclusion: Schizophrenia and ONOP are the only SMI subtypes associated with adverse clinical outcomes after AMI. However, all patients with SMI were less likely to receive invasive management for AMI, with female gender and schizophrenia diagnosis being the strongest predictors of conservative management. A multidisciplinary approach between psychiatrists and cardiologists could improve the outcomes of this high-risk population.

Résultats : Sur un total de 6 968 777 hospitalisations pour un IAM entre 2004 et 2014, 439 544 patients (6,5 %) avaient reçu un diagnostic de TMG. Même si les patients atteints de schizophrénie et d'ATPNO affichaient des taux bruts de mortalité hospitalière et d'accident vasculaire cérébral (AVC) plus élevés que ceux sans TMG, seuls les patients schizophrènes présentaient une probabilité de mortalité plus élevée (RC : 1,10; intervalle de confiance [IC] à 95 % : de 1,04 à 1,16), tandis que ceux du groupe ATPNO étaient les seuls à avoir une probabilité d'AVC plus élevée (RC : 1,53; IC à 95 % : de 1,42 à 1,65) après ajustement multivarié. Les patients de la catégorie ATPNO étaient les seuls à présenter une probabilité d'hémorragie pendant l'hospitalisation plus élevée que ceux sans TMG (RC : 1,11; IC à 95 % : de 1,04 à 1,17). Les patients atteints d'un TMG, quel que soit son sous-type, étaient tous moins susceptibles de subir une angiographie coronarienne ou une intervention coronarienne percutanée, et la probabilité de subir l'une ou l'autre de ces interventions était la plus faible dans le groupe des patients atteints de schizophrénie (RC : 0,46, IC à 95 % : de 0,45 à 0,48; et RC : 0,57, IC à 95 % : de 0,55 à 0,59, respectivement).

Conclusions : La schizophrénie et les ATPNO sont les seuls sous-types de TMG associés à des résultats cliniques défavorables après un IAM. Toutefois, les patients présentant un TMG étaient tous moins susceptibles de faire l'objet d'une prise en charge invasive de l'IAM et le sexe féminin et le diagnostic de schizophrénie étaient les prédicteurs les plus robustes d'une prise en charge conservatrice. Une approche interdisciplinaire où psychiatres et cardiologues travailleraient en concertation pourrait améliorer les résultats dans cette population à risque élevé.

often excluded from clinical trials because of concerns about their adherence to cardiovascular medications and follow-up.[8] A nationwide analysis in patients with schizophrenia and bipolar disorder presenting with ST-elevation myocardial infarction (STEMI) demonstrated an increased mortality in patients with schizophrenia and reduced odds of revascularization in both subgroups.[9] Conversely, an analysis of elderly patients (> 65 years) presenting with AMI showed that patients with mental health disorders (schizophrenia, affective disorders, and substance abuse disorder) were not at increased risk of 30-day mortality, although they were also less likely to undergo coronary revascularization.[10]

Although previous studies have looked at the clinical outcomes of SMI in the context of AMI, they have demonstrated conflicting results and were subject to limitations such as analysis of selected cohorts (single acute coronary syndrome [ACS] subtype, eg, STEMI)[9] or a single geographical region (eg, State of Florida),[11] inclusion of selected outcomes (eg, only mortality),[12] exclusion of patients with previous myocardial infarction,[12] or the analysis of a small sample that may not be representative of the population of interest.[13] Furthermore, patients with SMI are a heterogeneous population with differences in their underlying pathophysiology and pharmacotherapy according to their diagnosis subtype that may lead to divergent effects on their clinical outcomes in the context of AMI. The majority of studies have investigated the overall effect of all-cause SMI[11,14,15] or analyzed individual mental health subtypes without a comparison of the relative risks of clinical outcomes according to SMI subtype.[10] Finally, although some studies have looked at gender differences in reperfusion therapy,[11,12,16] there have been no reports on differences in the clinical outcomes of patients with SMI after AMI according to gender.

The current study used a national cohort drawn from the National Inpatient Sample over an 11-year period (2004-2014) to define the prevalence of patients with SMI presenting with AMI and examine their clinical characteristics, in-hospital outcomes, and provision of care, stratified by subtype of SMI and further stratified by gender.

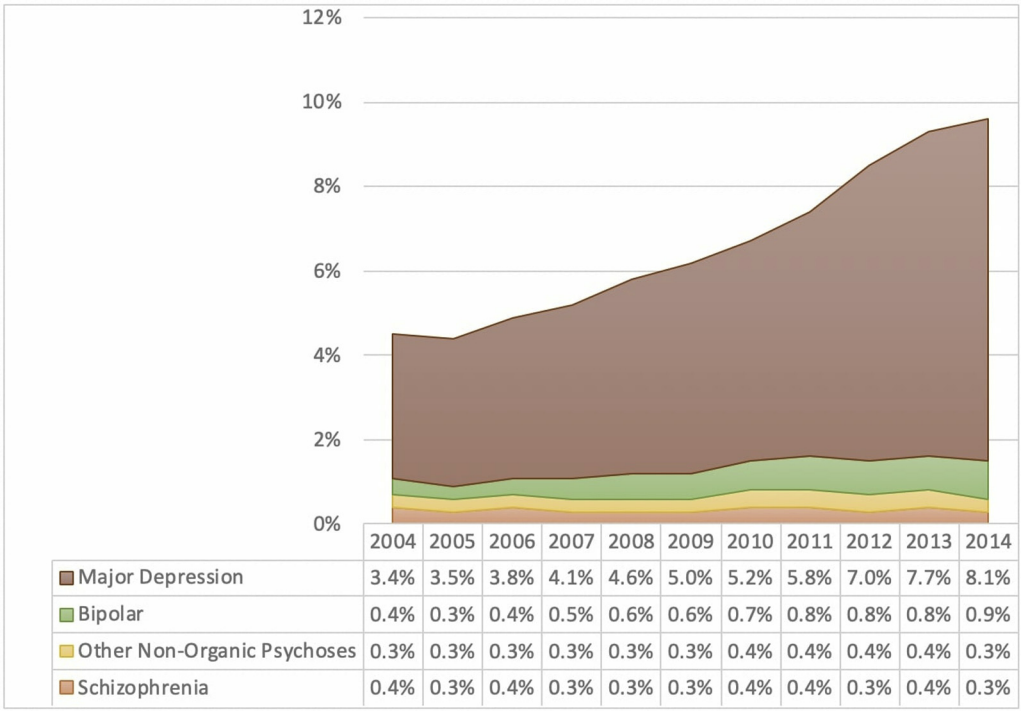
Methods

Data source

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project.[17] Further information about the design of NIS and its previous validation is available in Supplemental Appendix S1.

Study design and population

A retrospective observational analysis of all AMI hospitalizations between 2004 and 2014 from the NIS database was



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Major Depression	3.4%	3.5%	3.8%	4.1%	4.6%	5.0%	5.2%	5.8%	7.0%	7.7%	8.1%
Bipolar	0.4%	0.3%	0.4%	0.5%	0.6%	0.6%	0.7%	0.8%	0.8%	0.8%	0.9%
Other Non-Organic Psychoses	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.4%	0.4%	0.4%	0.4%	0.3%
Schizophrenia	0.4%	0.3%	0.4%	0.3%	0.3%	0.3%	0.4%	0.4%	0.3%	0.4%	0.3%

Figure 1. Prevalence of severe mental illness (SMI) from 2004 to 2014 according to subtype.

performed. Diagnoses and procedure variables were extracted using the relevant International Classification of Diseases, 9th Revision, Clinical Modification codes. The cohort was stratified into 5 groups: no SMI, schizophrenia, bipolar disorder, other non-organic psychoses (ONOP), and major depression. Further information on the methods used to identify patient characteristics and procedural data and to exclude missing cases is available in Supplemental Appendix S2 and Supplemental Table S1.

Outcomes

The primary outcome measures were to define the prevalence of SMI in AMI and examine the clinical characteristics, comorbidity burden, and in-hospital rates of major acute cardiovascular and cerebrovascular events (MACCE) (composite of mortality, acute stroke/transient ischemic attack [TIA], and cardiac complications) and all-cause bleeding. Cardiac complications included any pericardiocentesis, cardiac tamponade, hemopericardium, and coronary dissection during hospitalization, whereas bleeding was defined as any postprocedural hemorrhage or hematoma, or bleeding requiring transfusion.

The secondary outcome was the evaluation of the receipt of coronary angiography and revascularization (percutaneous coronary intervention [PCI] and coronary artery bypass grafting).

Statistical analysis

For detailed statistical analysis methods and a list of the covariates adjusted for, please refer to Supplemental Appendix S3.

Results

A total of 6,738,757 patients were included in the final analysis (Supplemental Fig. S1). Patients with a diagnosis of SMI comprised 6.5% (n = 439,544) of the study cohort. The patient characteristics of the study population are presented in Supplemental Table S2 according to the presence or absence of SMI and SMI subtype: schizophrenia (0.4%, n = 23,582), bipolar disorder (0.3%, n = 41,362), ONOP (0.6%, n = 22,359), and major depression (5.3%, n = 352,241), the latter being the most common subtype. The prevalence of SMI among the population with ACS doubled over the study period (from 4.5% in 2004 to 9.5% in 2014), primarily because of an increase in major depression and bipolar disorder diagnoses (Fig. 1), whereas the prevalence of ONOP and schizophrenia disorders has not changed. Several key differences in patient demographics are seen across the study groups (Supplemental Table S1, Supplemental Appendix S4).

Use of invasive management

There was a notable increase in the rates of both coronary angiography and PCI in all the groups over the study period (Supplemental Fig. S2). However, in comparison with patients without SMI, the rates of coronary angiography and PCI were persistently lower in all SMI subtypes except those with bipolar disorder, who overall were more likely to be offered coronary angiography (67.1% vs 64.4%, $P < 0.001$) (Fig. 2, Supplemental Table S4). In multivariate analysis, all SMI subtypes were associated with reduced odds of coronary angiography and PCI, with schizophrenic patients being the least likely to undergo either of the procedures (Fig. 3, Supplemental Table S6).

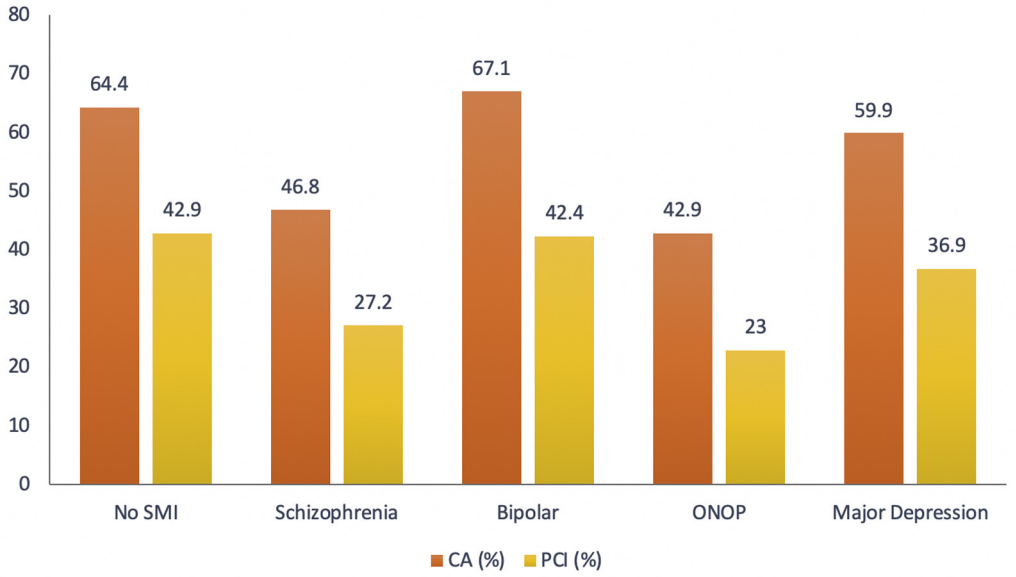


Figure 2. Receipt of coronary angiography and percutaneous coronary intervention (PCI). CA, coronary angiography; ONOP, other non-organic psychoses; SMI, severe mental illness.

The rates of coronary angiography and PCI were also lower among women across all study groups, including patients without an SMI diagnosis (Fig. 4), a finding that persisted in multivariate analysis (Supplemental Table S7). However, the odds of receipt of coronary angiography between genders were not significant in the schizophrenia and major depression groups.

In-hospital MACCE, mortality, and stroke

Patients with ONOP and schizophrenia experienced the highest rates of in-hospital MACCE (Fig. 5), primarily driven by higher rates of mortality (6.4% and 7.5%) and stroke (4.0% and 2.2%) compared with other SMI subtypes and patients without SMI ($P < 0.001$ for both). The lowest rates of MACCE, mortality, and stroke were observed in patients with bipolar disorder (Table 1).

In multivariate analysis, patients with ONOP and major depression were associated with significantly reduced odds of MACCE (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.82-0.90 and OR, 0.86; 95% CI, 0.85-0.88, respectively) (Fig. 3, Supplemental Table S6). However, both groups demonstrated a polar effect on stroke; patients with ONOP had a 53% increased odds of stroke, and patients with major depression had a 16% reduced odds of stroke. There was no difference in either outcome (MACCE and stroke) in patients with schizophrenia and bipolar disorder. Schizophrenia was the only subtype associated with increased odds of mortality (OR, 1.10; 95% CI, 1.04-1.16), whereas all other SMI subtypes were associated with a significantly reduced odds of mortality.

In subgroup gender analysis, the rates of in-hospital MACCE, mortality, and stroke were consistently higher in women than in men, except the rates of stroke in ONOP, which were higher in men (Fig. 6, Supplemental Table S4). In multivariable analysis, the odds of MACCE were increased in women without SMI and those with bipolar disorder and major depression, primarily driven by increased odds of acute stroke in these groups (Supplemental Table S7). In contrast to the other groups, women with ONOP were associated with reduced odds of MACCE and stroke compared with men (Supplemental Table S7). Furthermore, women without SMI and those with ONOP and major depression were at reduced odds of mortality compared with men, whereas there was no difference in mortality between genders in the schizophrenia and bipolar disorder groups.

A temporal analysis of outcomes demonstrates an overall decline in the rates of MACCE, mortality, and acute stroke/TIA in all the study groups except the ONOP and bipolar disorder groups, whose rates of MACCE and acute stroke/TIA have increased or remained the same (Supplemental Table S5). However, the pattern of differences in rates of MACCE, mortality, and stroke between groups remained the same throughout the study period.

In-hospital bleeding

In comparison with patients without SMI, only the ONOP group experienced higher rates of bleeding, whereas all other SMI subtypes experienced lower rates of bleeding (Fig. 5). Subgroup gender analysis demonstrated higher rates of bleeding among women in those without SMI and those with schizophrenia and lower rates of bleeding among women in those with bipolar disorder and ONOP (Fig. 6). There was no difference in crude rates of bleeding between both genders in patients with major depression.

In multivariate analysis, only patients with ONOP were associated with an increased odds of bleeding (OR, 1.11; 95% CI, 1.04-1.17; $P = 0.001$), whereas all other SMI subtypes were at a significantly reduced odds of bleeding (schizophrenia: OR, 0.70; 95% CI, 0.65-0.75; bipolar disorder: OR, 0.85; 95% CI, 0.81-0.90; major depression: OR, 0.97; 95% CI, 0.95-0.98; $P < 0.001$ for all outcomes) (Fig. 3, Supplemental Table S6).

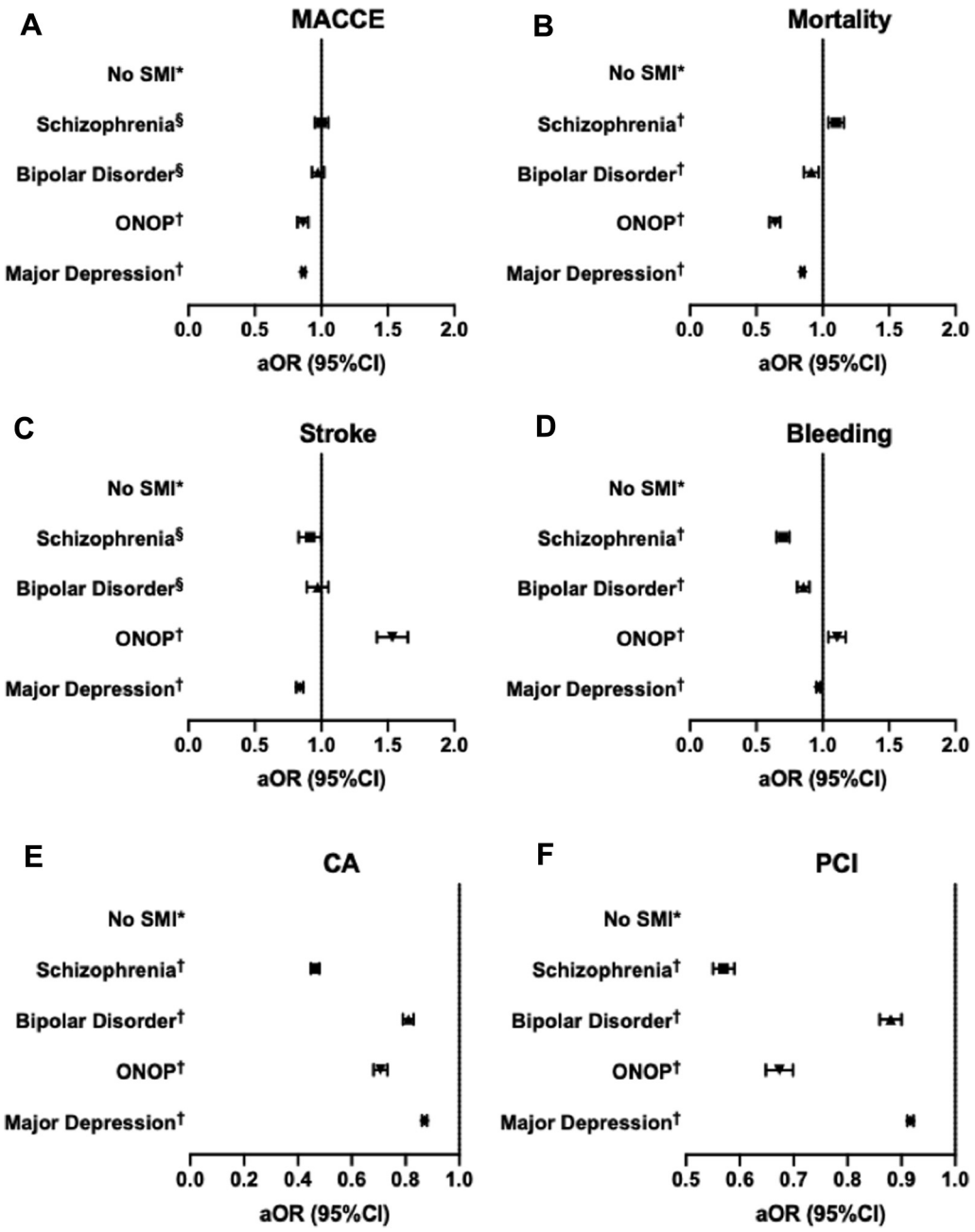


Figure 3. Odds ratio (OR) (95% CI) of adverse outcomes according to SMI subtype. *Reference group is no SMI. §Nonsignificant ($P \geq 0.05$). †$P < 0.001$. aOR, adjusted odds ratio; CA, coronary angiography; CI, confidence interval; MACCE, major acute cardiovascular and cerebrovascular events; ONOP, other non-organic psychoses; PCI, percutaneous coronary intervention; SMI, severe mental illness.

A multivariate analysis according to gender revealed increased odds of bleeding in women without SMI and in those with schizophrenia and major depression (Supplemental Table S7). In contrast, no difference in bleeding was found between genders in patients with ONOP, and women with bipolar disorder were at reduced odds of bleeding.

The rate of all-cause bleeding increased in all groups over the study period but remained higher in SMI groups compared with patients without SMI, with the exception of the ONOP group, whose rates of bleeding were higher than in patients without SMI (Supplemental Table S5).

Sensitivity analysis

A sensitivity analysis according to AMI type (STEMI vs non-STEMI) was performed to exclude examine differences in outcomes between both AMI presentations. Overall, the findings in the STEMI and non-STEMI groups were generally similar to those found in the total cohort (Supplemental Table S6). However, certain differences were observed within AMI subgroups. In the non-STEMI subgroup, patients with bipolar disorder were associated with reduced odds of MACCE compared with those without SMI, whereas there

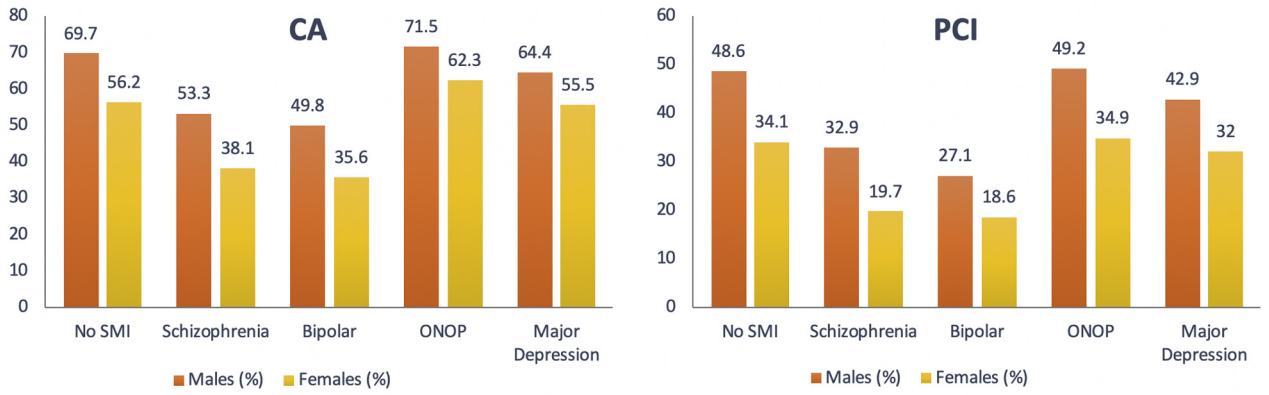


Figure 4. Receipt of coronary angiography and PCI according to SMI subtype and gender. CA, coronary angiography; ONOP, other non-organic psychoses; PCI, percutaneous coronary intervention; SMI, severe mental illness.

was no difference in MACCE and all-cause bleeding between patients without SMI and those with ONOP. In the STEMI subgroup, there was no difference in mortality and all-cause bleeding between patients with bipolar disorder and those without SMI, as was the case in all-cause bleeding between patients with major depression and those without SMI.

Discussion

Our findings in the present study, drawn from a national cohort of ACS hospitalizations in the United States, show a significant increase in the prevalence of patients with SMI presenting with AMI over the study period. We observe that patients with SMI represent a multi-morbid cohort with a higher cardiovascular risk and a more significant burden of comorbidities than those without SMI. Our results demonstrate significant disparities in the clinical outcomes and use of invasive strategies among patients with SMIs, including bipolar disorder, ONOP, schizophrenia, and major depression. Furthermore, we report lower rates of invasive management (coronary angiography and PCI) in patients with SMI, who experience higher crude rates of adverse outcomes, including MACCE, mortality, bleeding, and stroke, compared with those without an SMI diagnosis. However, after adjustment for confounders, patients with schizophrenia were associated with increased odds of in-hospital mortality among all SMI subtypes, whereas patients with ONOP were the only SMI group at increased odds of stroke and bleeding complications after AMI. Finally, our analysis highlights a gender gap in clinical outcomes and invasive management strategy, with women being less likely to be offered early invasive strategies (coronary angiography and PCI) despite their higher risk of mortality.

Patients with SMI are a heterogeneous group with a multitude of pathological and socioeconomic risk factors for

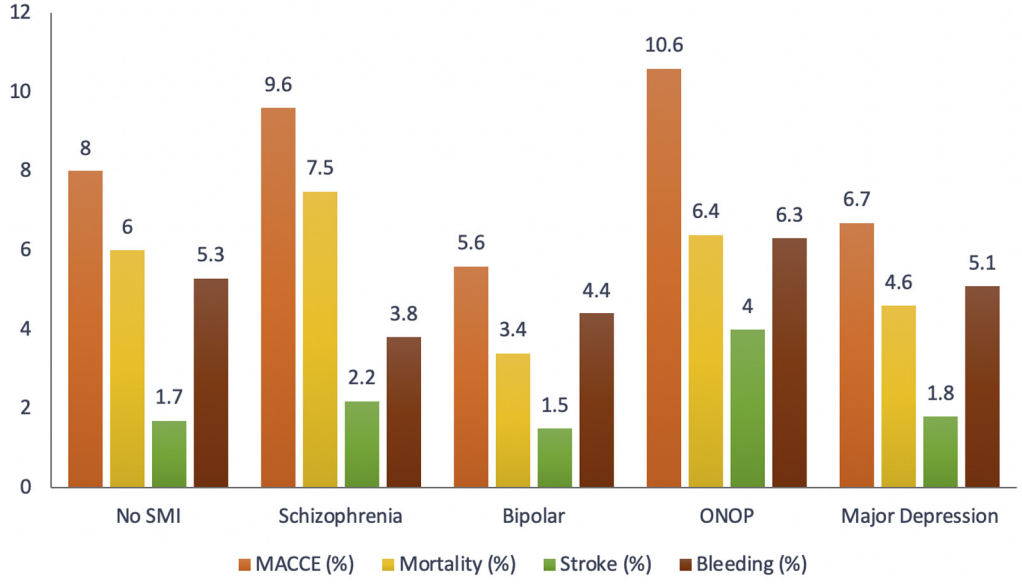


Figure 5. In-hospital adverse events according to SMI subtype. MACCE, major acute cardiovascular and cerebrovascular events; ONOP, other non-organic psychoses; SMI, severe mental illness.

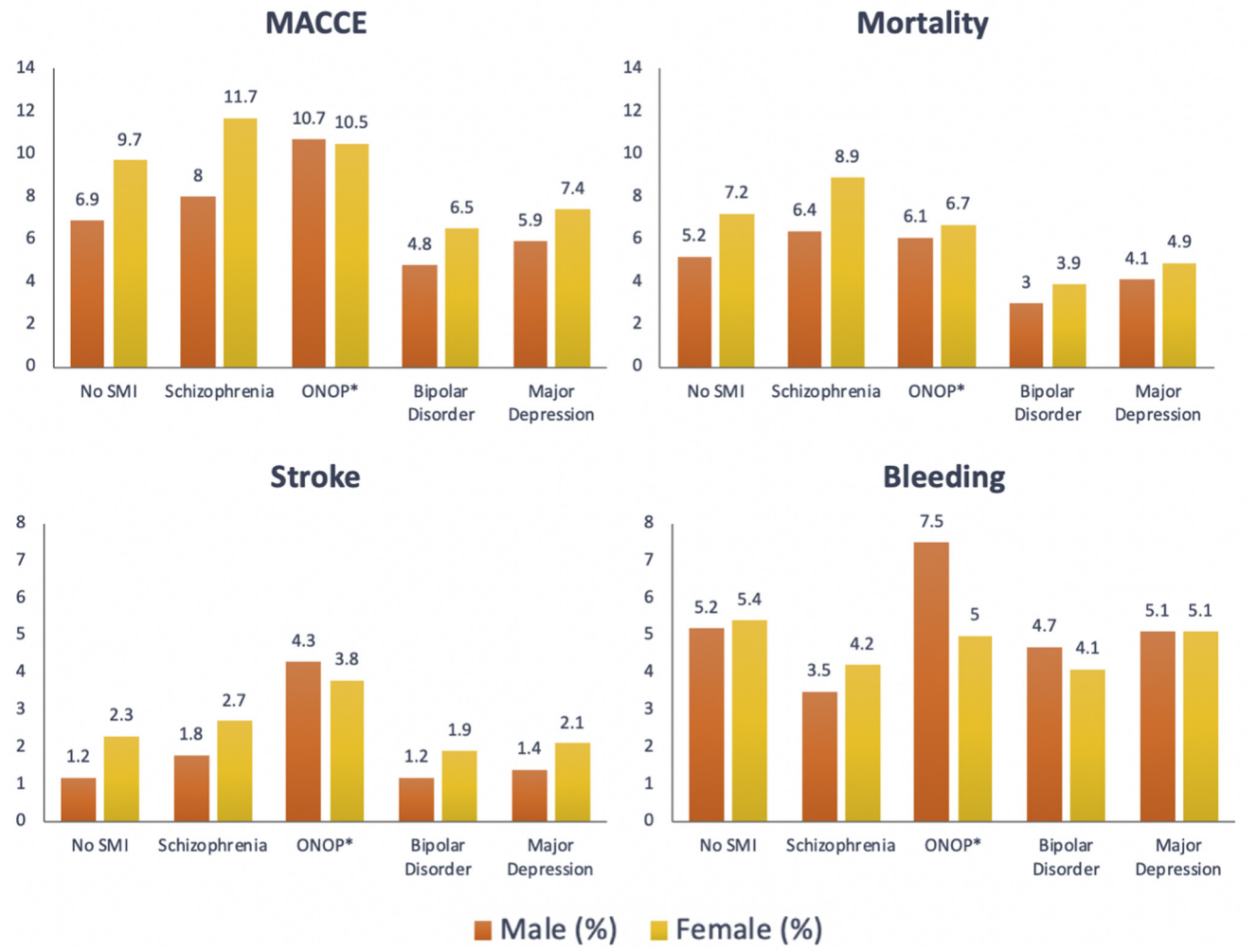


Figure 6. In-hospital adverse events according to gender. MACCE, major acute cardiovascular and cerebrovascular events; ONOP, other non-organic psychoses; SMI, severe mental illness.

CVD, depending on the subtype of SMI, and have been shown to have a higher burden of risk factors, such as diabetes, smoking, obesity, and chronic kidney disease.[18-23] Furthermore, their use of psychotropic medications, such as antipsychotics and selective serotonin reuptake inhibitors (SSRIs), places them at a higher risk of adverse outcomes, including stroke, cardiovascular mortality, and bleeding.[24-27] Antipsychotics and antidepressants such as SSRIs have been shown to increase the risk of metabolic syndrome because of their interaction with target 5-hydroxytryptamine neuroreceptors that modulate weight control and glucose metabolism, which increases the risk of myocardial infarction.[28-30] Furthermore, the use of antipsychotics (typical and atypical) has been associated with an increased risk of cerebrovascular events, especially in elderly patients, although the underlying mechanism remains unknown,[31,32] whereas SSRIs are thought to increase the uptake of serotonin into platelets leading to increased bleeding tendency.[33] In this national analysis of all hospitalizations with AMI in the United States, we show that only more complex SMI subtypes such as schizophrenia were at increased odds of in-hospital mortality. A previous national analysis of the **S**wedish **W**eb-System for **E**nhancement and **D**evelopment of **E**vidence-Based Care in **H**eart Disease **E**valuated **A**ccording to **R**ecommended **T**herapies (SWEDEHEART) registry also demonstrated higher mortality in patients with schizophrenia both at 30-day (OR, 2.58; 95% CI, 1.88-3.54) and 1-year (OR, 2.97; 95% CI, 2.39-3.69) follow-ups in patients admitted after AMI.[12] However, in contrast to our findings, patients with bipolar disorder (n = 442) were also shown to be at greater odds of mortality in their analysis, albeit only significant at 1-year follow-up (OR, 1.62; 95% CI, 1.20-2.20). In contrast, an analysis of approximately 800 veterans with SMI showed lower crude rates of 30-day mortality (4.6% vs 6.2%) and higher 1-year mortality (15.3% vs 13.2%) in patients with SMI compared with those without any mental illness.[14] Although their findings did not reach statistical significance, the marked difference in results between studies highlights the limitations of analyzing small and combined cohorts of all SMI. More important, not all the SMI subtypes are associated with increased mortality hazard in our analysis, with certain SMI subtypes such as bipolar disorder and major depression being at lower odds of in-hospital mortality compared with those without SMI.

Table 1. In-hospital clinical outcomes and quality indicators according to subtype of SMI

	No SMI	Schizophrenia	ONOP	Bipolar disorder	Major depression	Total	*P* value
MACCE, %	8.0	9.6	10.6	5.6	6.7	7.9	< 0.001
Cardiac complications, %	0.7	0.4	0.6	0.8	0.6	0.7	< 0.001
Acute stroke/TIA, %	1.7	2.2	4.0	1.5	1.8	1.7	< 0.001
Mortality, %	6.0	7.5	6.4	3.4	4.6	5.9	< 0.001
All-cause bleeding, %	5.3	3.8	6.3	4.4	5.1	5.2	< 0.001
Use of assist device or IABP, %	5.0	4.0	4.9	3.9	3.3	4.9	< 0.001
Shock, %	5.0	6.1	5.4	4.0	3.6	4.9	< 0.001
Receipt of coronary angiography, %	64.4	46.8	42.9	67.1	59.5	64.0	< 0.001
Receipt of PCI, %	42.9	27.2	23.0	42.4	36.9	42.5	< 0.001
Receipt of CABG, %	8.5	5.4	10.9	7.0	6.9	8.4	< 0.001
Discharge against medical advice (%)	0.8	2.5	1.5	2.7	0.8	0.8	< 0.001

CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; MACCE, major adverse cardiovascular and cerebrovascular events (composite of mortality, acute stroke/transient, and cardiac complications); ONOP, other non-organic psychoses; PCI, percutaneous coronary intervention; SMI, severe mental illness; TIA, transient ischemic attack.

To the best of our knowledge, no previous study has examined stroke and bleeding outcomes in patients with SMI after AMI. Our findings show that only patients with ONOP were at increased odds of bleeding and stroke, whereas all other SMI subtypes (bipolar disorder, schizophrenia, and major depression) were at lower odds of both outcomes compared with no SMI. A plausible explanation could be the greater use of psychotropic medications in patients with psychosis, which is known to be associated with increased odds of adverse cardiovascular events, especially in elderly patients, although the underlying mechanism remains unknown.[31,32] Likewise, the use of SSRIs is known to promote the uptake of serotonin into platelets, leading to an increase in bleeding tendency.[33] The lower frequency of stroke and bleeding in SMI subtypes other than ONOP could be explained by the low rates of invasive coronary management in these patients. Although we have adjusted for the differences in patient demographics and receipt of revascularization, there could be residual unmeasured confoundment that accounts for these findings.

Our gender subgroup analysis highlights persistent differences in invasive management strategies and in clinical outcomes of patients with and without SMI. We found women in all study groups to be associated with lower or insignificant odds of mortality compared with men, but also at increased odds of acute stoke/TIA, except in those with ONOP, in whom there was no difference between genders. Women with schizophrenia were also associated with the highest odds of bleeding complications compared with men. However, women of all subgroups were less likely to undergo invasive management compared with men, especially women with bipolar disorder, who were 15% and 34% less likely to receive coronary angiography and PCI, respectively. Despite the lack of evidence on gender outcomes in this population, a possible explanation for our findings is the higher prevalence of comorbidities predisposing to bleeding and stroke among women, as seen in our patients' demographics. However, the disparities in clinical outcomes according to gender highlight the need for prospective studies to explore the underlying pathophysiological mechanisms that may lead to these differences in patients with SMI.

The present study is the first to examine the prevalence of SMI in the AMI population and shows an increase in the prevalence of SMI over an 11-year horizon, primarily due to increasing rates of major depression and bipolar disorder diagnoses. Although these findings are in keeping with previous reports of trends in the general population,[34-36] it is possible that that these diagnoses have been coded more frequently in later years because of physicians' awareness of their implications in the context of AMI hospitalizations.

The lower rates of invasive management (coronary angiography and PCI) in patients with SMI may be due to several reasons. It is possible that patients with SMI lack the ability to engage in the discussions required for informed consent for such procedures. Furthermore, their lack of recognition and diagnostic overshadowing in emergency services lead to delayed presentations of their AMI. Patients undergoing PCI are committed to a minimum duration of dual antiplatelet therapy, as well as other secondary prevention pharmacotherapy, regular follow-up, and access to cardiac rehabilitation, to optimize their response to pharmacotherapy and success of their coronary intervention.[37,38] However, patients with SMI are previously reported to have poor compliance with diet advice, cardiac medications, and rehabilitation, which often leads to physicians' reluctance to offer them coronary intervention.[4,10,15] Consequently, patients with SMI who do not undergo in-hospital invasive management are at an even greater risk of adverse clinical outcomes after AMI, including higher rates of mortality and future reinfarction.[37-39] However, few studies have compared these management strategies across different SMI subtypes, whereas the majority have examined the association of all-cause SMI with odds of reperfusion therapy.[10,11,15] For example, Campi et al.[11] reported reduced odds of reperfusion therapy (PCI, thrombolysis, or coronary artery bypass grafting; OR, 0.70; 95% CI, 0.60-0.80) in patients with charted mental illnesses (composite of schizophrenia, bipolar, and depressive disorders; n = 1036) presenting with AMI across the state of Florida. Although these findings were significant, they did not inform of SMI subgroups with the least odds of receiving invasive coronary management. We show that patients with SMI of all subtypes were consistently less likely to be offered an invasive management strategy (coronary angiography and PCI) over the study decade.[40,41] The lowest odds of invasive management (coronary angiography and PCI) were in patients with schizophrenia, although they were at the greatest risk of mortality in our study. An individualized patient-based approach is required to assess these complex patients to improve the use of guideline-recommended therapy in this high-risk group.

Limitations

There are several limitations to the present study. First, the NIS is an administrative dataset that is susceptible to coding. Although the identification of ACS and SMI diagnoses and comorbidities was based on the use of administrative codes, International Classification of Diseases, 9th Revision codes have been validated for the purposes of cardiovascular research.[42,43] Second, the ischemic benefits of an invasive strategy over a conservative management of AMI have been primarily shown in studies reporting at least 30-day follow up.[39,44,45] Therefore, it is possible that patients with SMI experience worse clinical outcomes in the long term than those reported in the present study, which only captures in-hospital outcomes. Third, because the NIS dataset does not capture pharmacotherapy, we were unable to determine differences in the use of antithrombotic therapy between the study groups. Finally, we have not been able to assess the severity of the mental illness or the overlap of mental health diagnoses, which remain as potential residual confounders. Nevertheless, we believe that our findings provide insight into the real-world, in-hospital clinical outcomes of a large and unselected ACS cohort with SMI.

Conclusion

Our analysis of a national cohort of ACS hospitalizations shows a disparity of clinical outcomes among patients with SMI and identifies patients with schizophrenia and ONOP as those with the poorest outcomes, namely, higher in-hospital mortality and in-hospital stroke, respectively. Furthermore, we conclude that patients with SMI are less likely to be offered an invasive management strategy, with women with all SMI subtypes and patients with schizophrenia being the most disadvantaged groups.

Funding Sources

M.O.M. receives PhD studentship funding from Medtronic Ltd.

Disclosures

D.S. is an expert advisor to the National Institute for Health and Care Excellence (NICE) for guidelines, a member of the current NICE guideline development group for rehabilitation in adults with complex psychosis and related severe mental health conditions, and a board member of the National Collaborating Centre for Mental Health. The stated views are personal and not those of the NICE or National Collaborating Centre for Mental Health.

References

1. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 2013;70:931-9.

2. Laursen TM, Wahlbeck K, Hallgren J, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. PLoS One 2013;8:e67133.

3. Laursen TM, Nordentoft M. Heart disease treatment and mortality in schizophrenia and bipolar disorder - changes in the Danish population between 1994 and 2006. J Psychiatr Res 2011;45:29-35.

4. Osborn DJ, Levy G, Nazareth I, et al. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom general practice research database. Arch Gen Psychiatry 2007;64:242-9.

5. Kessler RC, Aguilar-Gaxiola S, Alonso J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiol Psichiatr Soc 2009;18:23-33.

6. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health Vol 2019. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, 2017.

7. Wu S-I, Chen S-C, Liu S-I, et al. Relative risk of acute myocardial infarction in people with schizophrenia and bipolar disorder: a population-based cohort study. PLoS One 2015;10:e0134763.

8. Kanuch SW, Cassidy KA, Dawson NV, et al. Recruiting and retaining individuals with serious mental illness and diabetes in clinical research: lessons learned from a randomized, controlled trial. J Health Dispar Res Pract 2016;9:115-26.

9. Schulman-Marcus J, Goyal P, Swaminathan RV, et al. Comparison of trends in incidence, revascularization, and in-hospital mortality in ST-elevation myocardial infarction in patients with versus without severe mental illness. Am J Cardiol 2016;117:1405-10.

10. Druss BG, Bradford DW, Rosenheck RA, Radford MJ, Krumholz HM. Mental disorders and use of cardiovascular procedures after myocardial infarction. JAMA 2000;283:506-11.

11. Campi TR Jr, George S, Villacís D, et al. Effect of charted mental illness on reperfusion therapy in hospitalized patients with an acute myocardial infarction in Florida. Medicine (Baltimore) 2017;96:e7788.

12. Bodén R, Molin E, Jernberg T, et al. Higher mortality after myocardial infarction in patients with severe mental illness: a nationwide cohort study. J Intern Med 2014;277:727-36.

13. Attar R, Berg Johansen M, Valentin JB, Aagaard J, Jensen SE. Treatment following myocardial infarction in patients with schizophrenia. PLoS One 2017;12:e0189289.

14. Petersen LA, Normand S-LT, Druss BG, Rosenheck RA. Process of care and outcome after acute myocardial infarction for patients with mental illness in the VA health care system: are there disparities? Health Serv Res 2003;38:41-63.

15. Li Y, Glance LG, Lyness JM, et al. Mental illness, access to hospitals with invasive cardiac services, and receipt of cardiac procedures by Medicare acute myocardial infarction patients. Health Serv Res 2012;48:1076-95.

16. Parashar S, Rumsfeld JS, Reid KJ, et al. Impact of depression on sex differences in outcome after myocardial infarction. Circ Cardiovasc Qual Outcomes 2009;2:33-40.

17. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality, 2012. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed June 5, 2019.

18. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA 2011;306:1241-9.

19. Birkenaes AB, Opjordsmoen S, Brunborg C, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry 2007;68:917-23.

20. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005;80:45-53.

21. De Hert M, Correll CU, Solmi M, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2017;16:163-80.

22. Bahorik AL, Satre DD, Kline-Simon AH, Weisner CM, Campbell CI. Serious mental illness and medical comorbidities: findings from an integrated health care system. J Psychosom Res 2017;100:35-45.

23. Zolezzi M, Abdulrhim S, Isleem N, Zahrah F, Eltorki Y. Medical comorbidities in patients with serious mental illness: a retrospective study of mental health patients attending an outpatient clinic in Qatar. Neuropsychiatr Dis Treat 2017;13:2411-8.

24. Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. Am J Psychiatry 2016;173:600-6.

25. Straus SM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the risk of sudden cardiac death. Arch Intern Med 2004;164:1293-7.

26. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ 2008;337:a1227.

27. Jiang H-Y, Chen H-Z, Hu X-J, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2015;13:42-50.e43.

28. Casey DE, Zorn SH. The pharmacology of weight gain with antipsychotics. J Clin Psychiatry 2001;62(Suppl 7):4-10.

29. Citrome L, Jaffe A, Levine J, Allingham B, Robinson J. Relationship between antipsychotic medication treatment and new cases of diabetes among psychiatric inpatients. Psychiatr Serv 2004;55:1006-13.

30. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010;71:1259-72.

31. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. BMJ 2005;330:445.

32. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335-41.

33. Hallbäck I, Hägg S, Eriksson AC, Whiss PA. In vitro effects of serotonin and noradrenaline reuptake inhibitors on human platelet adhesion and coagulation. Pharmacol Rep 2012;64:979-83.

34. Sara GE, Malhi GS. Trends in diagnosis of bipolar disorder: have the boundaries changed? Aust N Z J Psychiatry 2015;49:1021-8.

35. Weinberger AH, Gbedemah M, Martinez AM, et al. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychol Med 2018;48:1308-15.

36. Jeuring HW, Comijs HC, Deeg DJH, et al. Secular trends in the prevalence of major and subthreshold depression among 55–64-year olds over 20 years. Psychol Med 2018;48:1824-34.

37. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.

38. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139-228.

39. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, et al. Immediate versus delayed invasive intervention for non-STEMI patients: the RIDDLE-NSTEMI Study. JACC Cardiovasc Interv 2016;9:541-9.

40. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.

41. Jneid H, Addison D, Bhatt DL, et al. 2017 AHA/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol 2017;70:2048-90.

42. Birman-Deych E, Waterman AD, Yan Y, et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43:480-5.

43. DeShazo JP, Hoffman MA. A comparison of a multistate inpatient EHR database to the HCUP Nationwide Inpatient Sample. BMC Health Serv Res 2015;15:384.

44. Borgia F, Goodman SG, Halvorsen S, et al. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. Eur Heart J 2010;31:2156-69.

45. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998;32:1312-9.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.04.021.