**Myocardial infarction after acute ischaemic stroke: incidence, mortality, and risk factors**

**Running head:** Post-stroke MI incidence and outcomes

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**ABSTRACT**

**Objectives:** To determine the risk factor profiles associated with post-acute ischaemic stroke (AIS) myocardial infarction (MI) over long-term follow-up.

**Methods:** This observational study includes prospectively identified AIS patients (n=9840) admitted to a UK regional centre between January 2003-December 2016 (median follow-up: 4.72 years). Predictors of post-stroke MI during follow up were examined using logistic and Cox regression models for in-hospital and post-discharge events, respectively. MI incidence was determined using a competing risk non-parametric estimator. The influence of post-stroke MI on mortality was examined using Cox regressions.

**Results:** Mean age (SD) of study participants was 77.3(12.2) years (48% males). Factors associated with in-hospital MI (OR(95%CI)) were increasing blood glucose (1.80(1.17-2.77) per 10mmol/L), total leukocyte count (1.25(1.01-1.54) per $10x10^9$/L), and CRP (1.05(1.02-1.08) per 10mg/L increase). Age (HR(95%CI) =1.03(1.01-1.06)), coronary heart disease (1.59(1.01-2.50)), chronic kidney disease (2.58(1.44-4.63)), and cancers (1.76(1.08-2.89)) were associated with incident MI between discharge and one year follow-up. Age ((1.02(1.00-1.03)), diabetes (1.96(1.38-2.65)), congestive heart failure (2.07(1.44-2.99), coronary heart disease (1.81(1.31-2.50)), hypertension (1.86(1.24-2.79)), and peripheral vascular disease (2.25(1.40-3.63)) were associated with incident MI between 1-5 years after discharge. Diabetes (2.01(1.09-3.72)), hypertension (3.69(1.44-9.45)), and peripheral vascular disease (2.46(1.02-5.98)) were associated with incident MI between 5-10 years after discharge. Cumulative MI incidence over 10 years was 5.4%. MI during all follow-up periods (discharge-1 year, 1-5 years, 5-10 years) was associated with increased risk of death (respective HR(95%CI)=3.26(2.51-4.15), 1.96(1.58-2.42) and 1.92(1.26-2.93)).

**Conclusions:** In conclusion, prognosis is poor in post-stroke MI. We highlight a range of potential areas to focus preventative efforts.

## 1. INTRODUCTION

Ischaemic heart disease and stroke are the two leading causes of mortality worldwide, accounting for approximately 8.76 million and 6.24 million deaths respectively in 2015 [1,2]. Given the shared risk factor profile between stroke and cardiovascular disease, it has been suggested that stroke patients may have an elevated risk for myocardial infarction (MI) and non-stroke vascular death [3]. Nevertheless, real world data suggest that the incidence of MI after AIS may not be as high as theoretically expected. In a systematic review of 39 studies in patients with first transient ischaemic attack (TIA) or stroke, annual risks were 2.2% (95% CI: 1.7 to 2.7) for total MI, 0.9% (0.7 to 1.2) for non-fatal MI and 1.1% (0.8 to 1.5) for fatal MI [4]. Another meta-analysis showed similar results: ischaemic stroke was shown to be associated with an overall risk of MI in the year following stroke of 3% (1.0-5.0) [5]. The most recent systematic review calculated that the yearly risk of post-stroke MI is 1.67% [6].

Given that there is significant overlap between stroke secondary preventative therapies and acute coronary syndrome (ACS) primary prevention, it may not seem surprising that the annual incidence of post-stroke MI is not as high expected in such a highly co-morbid population. In fact, the aforementioned figures are comparable to those of incident ACS in the general population [7]. Nevertheless, it would be reasonable to expect that the epidemiology of MI may still be markedly different in AIS patients. It has been shown in a recent study that MI-associated hospital mortality is significantly higher in AIS patients than in non-AIS controls: 21.44% versus 7.1%, respectively [8]. Furthermore, it may be the case that the risk factors for post-AIS MI may differ significantly from those in the general population.

Whilst previous meta-analyses yielded risk profiles for post-AIS MI [4,6], these results may not be applicable in real-world setting, given that they originate from the pooling of highly heterogeneous data with a potentially high risk of bias, introduced by between-study differences such as the use of different stroke secondary prevention strategies.

In this study, we aimed to provide real-world data to clinical practice in the United Kingdom (UK) using a large British regional prospective stroke registry. More specifically, we aimed to determine the specific risk factor profiles associated with incident MI events in AIS patients at well-defined and clinically relevant time points: in-hospital and up to 1, 5 and 10 years after discharge. Furthermore, we also aimed to supplement current knowledge regarding the annual incidence rate of post-AIS MI and the influence of post-stroke MI events on patient mortality.

## 2. METHODS

Participants were drawn from the Norfolk and Norwich Stroke and TIA Register (NNSTR) database using previously defined selection criteria. The NNSTR is a prospective UK hospital-based register with a catchment population of approximately 750,000. Data collection methods have been reported previously [4,6]. The register received ethical approval from the Newcastle and Tyneside National Health Service (NHS) and Research Ethics Committee (12/NE/0170) as a research database. The protocol was approved by the Steering Committee of the Register. The study was conducted in accordance with the principles of the Declaration of Helsinki (1964) and later amendments.

Inclusion and exclusion criteria, outcomes of interests (MI incidence following AIS and mortality), and selection of study covariates were all agreed a-priori. A total of 10,776 patients were admitted with confirmed AIS between January 2003 and December 2016. Patients with missing post-discharge data (n = 214) and those lost during follow-up (n = 81) were excluded. As this was an incidence study of post-stroke MI, a further 641 patients having had an MI before the index AIS episode were excluded, yielding a total of 9840 patients included in the study (**Figure 1**).

In all participants, AIS was diagnosed based on evidence from patient history, neurological examination, and neuroimaging results. Follow-up data were collected in June 2017, allowing minimum follow-up of 6 months (median follow-up (95%CI) – 4.72 (4.62-4.82) years; total follow-up: 40,374 person-years). The median follow-up and the 95% confidence intervals were calculated using the reverse Kaplan-Meier method [9]. Record linkage with the UK NHS system ensures a robust ascertainment of co-morbidities and complete follow up data. Information on the incidence of post-stroke MI (the primary outcome for this study) were retrieved from the Norfolk and Norwich University Hospital's patient administration database, identified from codes in the 10th revision of the International Classification of Disease (ICD-10), based on patient history, ECG findings, and cardiac troponin levels (ICD I21; ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction). Since data were obtained by cross-linking the hospital database with NHS primary care data, all incident MI events occurring during the follow-up period were recorded unless they occurred outside the United Kingdom and were not recorded within the NHS primary care database.

Characteristic data and relevant covariates were selected based on existing literature [10-12] and clinical judgement. Data on age, sex, Oxfordshire Community Stroke Project (OCSP) classification (total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), posterior circulation stroke (POCS), lacunar stroke (LACS)), and relevant biochemical and haematological measurements collected on admission (random plasma glucose, haemoglobin, total white cell count, albumin, creatinine, urea, CRP (C-reactive protein), gamma-glutamyl transferase, and INR (International Normalised Ratio)) were collected by electronic record linkage. Information on pre-existing chronic cardiovascular and non-cardiovascular comorbidities were identified from ICD-10 codes based on clinical findings and retrieved from the hospital's administration database (diabetes (ICD E10-E14),

heart failure (I50), atrial fibrillation (I48), coronary heart disease (I20-I25), chronic kidney disease (N18), hypertension (I10-I15), dyslipidaemia (E78), peripheral vascular disease (I73.9), cancer (C00-C99), and TIA (G45)). Co-morbidities diagnosed during and after hospital admission were identified in the same manner. Co-morbidities were extracted as dichotomous variables from the NNSTR along with the time before or after the first stroke hospitalisation when they were first diagnosed. We extracted single entries representing the first-ever stroke presentation in the register for each patient and coded for subsequent admissions as a separate potentially confounding covariate.

Data were analysed using Stata 14 (StataCorp. 2015: Stata Statistical Software Release 14. College Station, TX: StataCorp LP). Descriptive statistics were generated for patients with and without incident MI during hospital stay and after discharge. Results were compared using independent-sample t-tests, Mann-Whitney U test, and Chi-squared test as appropriate.

*In-hospital risk factor analysis*

A binomial logistic regression model was employed to predict the risk factors of in-hospital MI. Age, sex, OCSP, co-morbidities, and blood results were used as covariates. The model was adjusted for age, sex and those co-morbidities and blood results reaching the 10% threshold of statistical significance in a stepwise forward selection model. Random plasma glucose on admission was highly correlated with diabetes ($r_s$=0.62), and therefore was not included as a covariate (model A). A further logistic regression model (Model B) was constructed to include random plasma glucose instead of pre-existing diabetes.

*Long-term risk factor analysis*

The association between co-morbidities and MI incidence during follow-up (discharge to 1 year, 1 to 5 years, and 5 to 10 years) was examined using Cox regressions to calculate cause-specific hazard ratios. The primary outcome of the regression models was incident MI (fatal or non-fatal), whilst death or end of follow-up were used as censoring events. Since incident MI and death are not independent events, cause-specific proportional hazards models were employed, as recommended by the previous literature in etiological studies [13]. Separate analyses were performed for each follow up period with subsequent models excluding patients who suffered an MI or for whom follow-up ended during the preceding period. This approach allowed us to consider the changing risk profile with older age after stroke as well as newly identified co-morbid chronic diseases and their impact on subsequent MI incidence. Co-morbid predictors were selected using a stepwise forward model using the threshold of 10% statistical significance (**Supplementary Table 1).** Further adjustment for the antiplatelet and anticoagulant medications prescribed after the acute event was performed in all survival models. To account for pre-existing co-morbidities and for those diagnosed during the follow-up, we introduced co-morbidity variables as binary time-updated variables.

*Post-stroke MI incidence*

MI incidence was calculated both for MI occurring during admission, and for all further events across follow-up. Cumulative incidence was calculated as the ratio of events over the total cohort size for the respective period. A cumulative incidence function was computed with incident MI as the outcome, death as the competing event and end of follow-up as the censoring event. Mean incidence rates for each predefined follow-up period were calculated by computing the average value of slope of the incidence function over the respective timeframe.

*Influence of MI on survival*

The Kaplan-Meier estimator was utilised to examine survival curves over the entire follow-up period stratified by a dichotomous variable coding for the incidence of MI during hospital admission. The survival functions were compared using the log-rank test. Cox regression models were constructed to estimate the effect on mortality that a diagnosis of MI in AIS patients had during each of the three pre-defined follow-up periods (discharge to 1 year, 1-5 years and 5 to 10 years). All models were adjusted for age, sex, OCSP, and comorbidities. MI and all comorbidities were time-updated to account for the time during or after the hospital stay when they were diagnosed.

## 3. RESULTS

A flowchart of the patient cohort is shown in **Figure 1** (8164/9840 patients survived to hospital discharge; 6417, 2947, and 938 patients respectively were followed up at 1, 5, and 10 years). Given our strict exclusion criteria and the record linkage with the NHS primary care databases, all patients included in the study have full follow up information until either death or the end of December 2016.

Characteristics of patients at hospital admission and in those surviving to discharge are shown in **Table 1.** Mean age (SD) of study participants was 77.3(12.2) years and 48% of patients were male. Patients with MI in hospital (vs. no MI) were more likely to be older, suffer TACS, and have diabetes. They were also more likely to have higher INR, plasma glucose, urea, creatinine, CRP, white blood cell count, and lower albumin levels on admission. Patients diagnosed with MI after discharge (vs. no MI) were more likely to be older, have ischaemic stroke, lacunar subtype, diabetes, coronary heart disease, hypertension and dyslipidaemia. These patients also had higher urea, creatinine, CRP, and lower levels of

haemoglobin and albumin at the time of stroke admission. The number of cases with missing data for each variable included in the analysis are illustrated in **Supplementary Table 1**.

**Figure 1** illustrates the patient population. From a total of 9840 eligible patients admitted between January 2003 and December 2016 with a diagnosis of AIS, 135(1.37%) had an MI during hospital admission and a further 281(2.86%) during study follow up.

*In-hospital risk factor analysis*

Predictive factors for in-hospital MI are shown in **Table 2.** Model A (pre-existing diabetes mellitus, but not admission blood glucose data included in model) showed that total white cell count (per $10x10^9$/L) and CRP (per 10mg/L increase) were associated with increased odds of in-hospital MI (respective OR(95%CI)=1.21(1.02-1.43) and 1.06(1.03-1.08)). Covariates associated with in-hospital MI in Model B (admission blood glucose, but not pre-existing diabetes included in model) were random plasma glucose on admission (1.80(1.17-2.77) per 10mmol/L increase), total white cell count (1.25(1.01-1.54) per $10x10^9$/L increase), and CRP (1.05(1.02-1.08) per 10mg/L increase). The mean time between blood sample collection on admission and incident MI was 1423 days (~3.9 years).

*Long-term risk factor analysis*

Cause-specific hazard ratios from multivariable Cox regression examining predictors of incident MI following hospital discharge are shown in **Figure 2** (full data presented in **Supplementary Table 2**). Factors associated with incident MI between hospital discharge and one-year follow up were age (HR(95% CI)=1.03(1.01-1.06)), coronary heart disease (1.59(1.01-2.50)), chronic kidney disease (2.58(1.44-4.63)), and cancers (1.76(1.08-2.89)). During the 1 to 5 year follow up period, associated risk factors were older age ((1.02(1.00-1.03)), diabetes mellitus (1.91(1.38-2.65)), congestive heart failure (2.07(1.44-2.99), atrial

fibrillation 0.72(0.49-1.05)), coronary heart disease (1.81(1.31-2.50)), hypertension (1.86(1.24-2.79)), and peripheral vascular disease (2.25(1.40-3.63)). Regression results for 5-10 years showed associated multivariable hazard ratios for diabetes mellitus (2.01(1.09-3.72)), hypertension (3.69(1.44-9.45)), and peripheral vascular disease (2.46(1.02-5.98)).

*Post-stroke MI incidence*

Overall MI incidence across study follow-up was 4.23% and cumulative MI incidence was 5.40%. MI incidence ratio in our cohort was 54 incident cases per 10,000 patient-years **(Figure 3, Supplementary Table 3**). Incidence ratios for the individual follow-up periods respectively were 63, 41, and 63 new cases per 10,000 patient-years (discharge to 1 year, 1-5 years, and 5-10 years).

*Influence of MI on survival*

Mortality during follow-up was higher amongst patients with in-hospital MI **(Supplementary Figure 1)** (Log-Rank test: $\chi^2$=18.6, df=1, $P$ <0.001). Cumulative mortality at predefined time periods in patients with and without in-hospital MI respectively was 31.1% vs 17.0% at 1 year, 57.8% vs. 34.6% at 5 years and 65.1% vs 44.8% at 10 years **(Supplementary Table 4)**. A diagnosis of MI during any time of the follow-up (0-10 years) was associated with increased risk of death (HR(95%CI)=2.30(1.95-2.70) **(Supplementary Table 5)**. MI during pre-defined follow up periods (discharge to 1 year, 1 to 5 years and 5 to 10 years) was also associated with increased risk of death (respective HR(95%CI)=3.26(2.51-4.15),1.96(1.58-2.42) and 1.92(1.26-2.93)).

## 4. DISCUSSION

Our analysis shows that whilst well recognised co-morbid risk factors for ACS were not predictive of in-hospital MI, elevated inflammatory markers were positively associated with the outcome, thus confirming the applicability of this previously defined relationship [14,15] in AIS. Nevertheless, an idiosyncratic finding of our analysis was that pre-existing diabetes mellitus was associated at the univariable level with reduced odds of MI in hospital (data not shown).Our model replacing a known pre-existing diagnosis of diabetes mellitus with the measured random plasma glucose on admission shows that patients with levels greater than 11.0 mmol/L (indicative of diabetes mellitus [16]) are at double odds of an in-hospital incidence MI, suggesting that diabetes may be underdiagnosed in our cohort. This finding also confirms the prognostic importance of admission hyperglycaemia in acute stroke patients in the context of MI [17].

Patients with CKD and cancers were more likely to have an MI in the first year after discharge. These conditions may have a more relentless progression than traditional cardiovascular co-morbidities, leading to earlier MI onset. Coronary heart disease was another predictive factor for MI within 1 year of discharge. On the other hand, patients exhibiting a more classical cardiovascular event risk phenotype (pre- or post-stroke diagnosis of peripheral vascular disease, coronary heart disease, heart failure, hypertension and diabetes) were more likely to suffer an MI between 1 and 5 years following AIS. Finally, hypertension and diabetes were the only predictors of MI during the time between 5 and 10 years after hospital discharge. The difference between the significant co-morbid risk factors in the medium (1-5 years) and long-term (5-10 years) follow-up may be explained by the fact that heart failure and atherosclerotic diseases are more likely to be less prevalent in our cohort in the long-term, given that patients with these co-morbidities have higher mortality rates [18].

It is also important to notice that gender was not a predictive factor for incident MI in any of our analyses, in contrast with the current knowledge of incident MI in healthy populations. Given that our cohort was only composed of stroke patients who were much older (mean age ~ 77 years), it is likely that the gender differences in MI incidence rates observed in younger ages would not be present [19,20].

The association between AIS and MI has been examined previously [6,10,21-29]. Nevertheless, these studies appear to yield different risk factor profiles, likely due to the high between-study heterogeneity, as indicated by the most recent meta-analysis [6]. This is not surprising, given that the epidemiology of AIS and post-stroke secondary preventative measures can vary worldwide [30]. Furthermore, most of these studies do not include in their analyses a full panel of potentially relevant co-morbid conditions or biochemical and haematological parameters. In the current study, we present an eloquent analysis based on a UK stroke population treated according to UK guidelines [31], which also performs additional adjustments for antithrombotic medications prescribed at discharge for stroke secondary prevention. Therefore, the results of our study may be utilised in clinical practice in the UK to determine the high-risk patient subgroups for post-AIS MI. Our study may have important implications in the era of personalised medicine since it provides a concrete list of co-morbidities which may require more intensive management to lower the risk of post-stroke MI. Our study also provides an important question for further research:whether the high-risk patient subgroups we have identified may benefit from different approaches in secondary prevention, such as anticoagulation.

Furthermore, we have demonstrated that incident MI increases the long-term mortality of AIS patients, with a more pronounced effect if occurring within 1 year after discharge. We have also calculated the annual post-AIS MI incidence rate to be 0.54%, roughly half of previously reported values [4-6]. These differences may relate to differences in post-stroke

secondary preventative measures between our cohort and other populations. It may also be the case that our competing risk non-parametric model yields better estimates. Nevertheless, our results are derived from real world data and it is likely that our estimates are accurate in the context of populations similar to our cohort receiving the same secondary prevention.

Our study benefits from several strengths. The cohort is a large prospectively identified population of hospitalised stroke patients. As a record linkage study embedded within the UK National Health Service (NHS) system, the ascertainment of co-morbidities is robust with only 2.74% of our initial cohort having been excluded due to missing follow-up information. Despite our study being performed as a retrospective analysis of a single-centre stroke registry, all stroke admissions were consecutive and recorded prospectively along with real-time co-morbid data. Thus, the selection bias in our cohort is likely to be minimal in comparison to other observational studies. We are the first study adjusting for the time of incident MI and comorbidity diagnoses in the time-to-event analyses. This statistical approach provides results which more closely model observed events. Furthermore, outcomes are examined in discrete time frames over the long-term, making adjustments for antithrombotic medications offered to stroke patients upon discharge. Thus, our statistical models account for confounding that may be introduced by the considerable overlap between stroke secondary prevention and MI primary prevention.

We acknowledge some limitations. Firstly, our study sample consisted mainly of a Caucasian population and therefore may not be applicable to other populations. Secondly, the documented prevalence of dyslipidaemia in our cohort appears to be significantly lower than the general British population [32]. Whilst it may be likely that this is driven by the adherence to lipid-lowering strategies in stroke patients at our centre, caution should be exerted when considering our results in populations with a higher burden of dyslipidaemia. Despite recording the date of death and relevant co-morbidities for each patient, we had no

information about the cause of death. We were therefore unable to examine cause-specific mortality. The information on acute MI extracted from the NNUSTR database did not discriminate between STEMI and NSTEMI. Thus, we have not been able to perform separate analyses for the two distinct clinical presentations which may have different outcomes and predictors. Finally, we only adjusted our time-to-event analyses for discharge antithrombotic medications, but not for hypoglycaemic agents or statins. We have also not recorded any change to antithrombotic medications that may have occurred after discharge in the primary care setting.

## 5. CONCLUSION

We have determined the predictive factors for post-AIS MI at distinct time points: in-hospital and at 1, 5 and 10 years after discharge. Our results may be utilised to identify which conditions may require more scrupulous management. Further research may be needed to determine whether these high-risk patient subgroups may benefit from more aggressive preventative strategies. We have also determined that the incidence of post-AIS MI was lower, but nevertheless comparable, in our population than in previous reports and that these events have a significant adverse impact on the survival of AIS patients. Finally, given our large sample size and long follow-up time, we believe our data are generalisable to the UK population with a similar age distribution and stroke aetiological profile whose management conforms to the national guidelines.

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**Norfolk and Norwich Stroke Registry Steering Committee Collaborators: Anthony K Metcalfe, Kristian M Bowles.**

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**CONTRIBUTIONS**

PKM and JFP are co-PIs of the NNUSTR. JHB-S performed data linkage. PKM conceived the study. Data were analysed by TAP under the supervision of ADW, ABC, PKM, DJM. TAP, ADW and PKM drafted the paper and all of the authors contributed in writing the paper. PKM is the guarantor.

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## FIGURE LEGENDS

No. of figures: 2

Are there color figures? No

Figure captions:

**Figure 1.** Study population summary.

**Figure 2.** Predictors of acute myocardial infarction in AIS patients from Cox proportional hazard models. Dots represent Hazard Ratios (obtained using Cox regression models) with error bars (95% confidence interval) for each predictor. Results data shown were adjusted for: age, diabetes, heart failure, atrial fibrillation, coronary heart disease, chronic kidney disease, hypertension, dyslipidaemia, peripheral vascular disease, cancer, transient ischemic attack, and previous stroke.

**Figure 3.** Incidence curve illustrating the cumulative incidence of MI in the patient population over the entire follow-up period after hospital discharge.