International Journal of Cardiology

Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure

--Manuscript Draft--

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Abstract:	Background – Atrial fibrillation (AF) and heart failure (HF) carry a poor prognosis in acute ischaemic stroke (AIS). The impact of revascularisation therapies on outcomes in these patients is not fully understood. Methods –National Inpatient Sample (NIS) AIS admissions (January 2004-September 2015) were included (n=4,597,428). Logistic regressions analysed the relationship between exposures (neither AF nor HF-reference, AF-only, HF-only, AF+HF) and outcomes (in-hospital mortality, length-of-stay >median and moderate-to-severe disability on discharge), stratifying by receipt of intravenous thrombolysis (IVT) or endovascular thrombectomy (ET). Results - 69.2% patients had neither AF nor HF, 16.5% had AF-only, 7.5% had HF-only and 6.7% had AF+HF. 5.04% and 0.72% patients underwent IVT and/or ET, respectively. AF-only and HF-only were each associated with 75-85% increase in the odds of in-hospital mortality. AF+HF was associated with greater than two-fold increase in mortality. Patients with AF-only, HF-only or AF+HF undergoing IVT had better or at least similar in-hospital outcomes compared to their counterparts not undergoing IVT, except for prolonged hospitalisation. Patients undergoing ET with AF-only, HF-only or AF+HF had better (in-hospital mortality, discharge disability, all-cause bleeding) or at least similar (length-of-stay) outcomes to their counterparts not undergoing ET. Compared to AIS patients without AF, AF patients had approximately 50% and more than two-fold increases in the likelihood of receiving IVT or ET, respectively. Conclusions –We confirmed the combined and individual impact of co-existing AF or HF on important patient-related outcomes. Revascularisation therapies improve these outcomes significantly in patients with these comorbidities.
Suggested Reviewers:	Gregg Fonarow GFonarow@mednet.ucla.edu
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Response to Reviewers:	28 August 2020 Professor Paolo G. Camici Editor-in-Chief

International Journal of Cardiology

Subject: Revision of Manuscript ID IJC_2020_1732_R2

Dear Professor Camici,

We thank the editors for giving us the opportunity to re-submit a revised version of an original article entitled “Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure” to be considered for publication in the International Journal of Cardiology.

We provide below point-by-point responses to the comments made by the reviewer.

We also attached a tracked version of our manuscript. Given that this is a third revision, we have tracked our changes on a clean version of the manuscript submitted for the second revision.

On behalf of all co-authors, I would like to take the opportunity to thank the Editorial Board for considering our paper and the reviewers for their helpful comments.

We sincerely hope that the revised version will satisfy the reviewers and the editors, and that the revised manuscript will be acceptable in the current form. We look forward to hearing from you.

Yours sincerely,

Professor Phyo K Myint (corresponding author)
Clinical Chair in Old Age Medicine
For and on behalf of all co-authors

We have highlighted the changes in the text, where appropriate, as follows: (additions in blue, deletions in red):.

Comments from reviewers:
REVIEWER 5
- This manuscript is a large-scale cohort study of acute ischemic stroke patients. Implication on revascularization (Intravenous thrombolysis or endovascular thrombectomy) should be minimized in the conclusion because of the following reasons.
1) This is not a prospective intervention study, but a observational study
Response: Thank you very much for taking the time to review our manuscript. We appreciate and share the reviewer’s concerns about drawing clinical conclusions regarding the use of revascularisation therapies in these patient groups based on an observational study. We have thus modified the conclusions drawn from this study to reflect the fact that while our results drawn from observational data are encouraging, no direct clinical recommendations can be made based on these without further clinical trial data.

Under ABSTRACT, page 2, lines 21-24:

“Conclusions –We confirmed the combined and individual impact of co-existing AF or HF on important patient-related outcomes. Revascularisation therapies improve these outcomes significantly in patients with these comorbidities and should be offered routinely unless contra-indicated.”

Under CONCLUSIONS, page 17, lines 16-24:

“In this study of real-world data, AIS patients with co-morbid AF or HF undergoing IVT

had either better or comparable in-hospital adverse outcomes than their counterparts not undergoing IVT. There were no positive associations between AF or HF and adverse in-hospital outcomes amongst AIS patients undergoing ET. Therefore, Cco-morbid AF and/or HF should not solely represent a criterion against delivering IVT therapy to AIS patients. Furthermore,, while ET may be an effective therapeutic strategy to manage the excess risk of adverse short-term outcomes associated with AF and/or HF in AIS. Therefore, revascularisation therapies should be considered and offered routinely in acute ischemic stroke patients with these comorbidities unless contra-indicated."

The study HIGHLIGHTS have also been updated accordingly:

"
•We examined the impact of IVT and ET on stroke outcomes in patients with AF and HF
•Estimates were calculated for all US ischemic stroke admissions between 2004-2015
•AF and HF were associated with significantly worse in-hospital outcomes
•IVT/ET reduced the AF/HF-associated excess odds of adverse in-hospital outcomes
•IVT/ET should be offered routinelyconsidered in ischemic stroke patients with AF/HF if not contraindicated.
"

2) The authors did not compare effect sizes of revascularization therapy on outcomes among different patient groups. Therefore, it is unclear at present whether revascularization is more effective in a specific patient group of AF(+)HF(+) compared with AF(-)HF(-).
Response: Thank you for highlighting this issue. We share the reviewer's concern that a direct comparison between the effect sizes of the IVT/ET interaction terms across the different exposure groups is warranted. Such direct comparisons can be performed by comparing the magnitudes of each IVT/ET interaction terms. We have thus added the following supplementary table displaying the odds ratios and 95% confidence intervals of the IVT and ET interaction terms with each one of the three exposure groups:

Supplementary Table 7. Interaction terms between revascularisation therapy (intravenous thrombolysis or endovascular thrombectomy) and the relationship between the exposures of interest and in-hospital outcomes (also see Supplementary Table 6).

	AF only	HF only	AF+HF
IVT Interaction Term			
In-Hospital Mortality	0.75 (0.67-0.84)	0.75 (0.62-0.89)	0.65 (0.56-0.76)
Los > Median	1.23 (1.14-1.32)	1.07 (0.95-1.20)	1.16 (1.04-1.30)
Discharge Disability	0.96 (0.89-1.04)	0.92 (0.81-1.05)	0.95 (0.82-1.10)
All-cause Bleeding	0.87 (0.78-0.97)	0.89 (0.74-1.07)	0.75 (0.64-0.88)
ET Interaction Term			
In-Hospital Mortality	0.40 (0.32-0.50)	0.41 (0.27-0.61)	0.34 (0.25-0.47)
Los > Median	0.70 (0.58-0.83)	0.96 (0.69-1.34)	0.65 (0.51-0.83)
Discharge Disability	0.59 (0.48-0.74)	0.75 (0.49-1.15)	0.76 (0.52-1.11)
All-cause Bleeding	0.56 (0.45-0.69)	0.54 (0.37-0.78)	0.52 (0.39-0.69)

IVT – Intravenous Thrombolysis, ET – Endovascular Thrombectomy
All regression models were adjusted for age, sex, ethnicity, smoking status, hospital characteristics (bed size, location, teaching status), 29 Elixhauser co-morbidities and other co-morbidities (myocardial infarction, coronary heart disease, other arrhythmias, dyslipidaemia, previous transient ischaemic attack, dementia, shock), previous coronary artery bypass surgery, and family history of cerebrovascular events or ischaemic heart disease.
Statistically significant ($P < 0.01$) results are displayed in Bold

Furthermore, the RESULTS and DISCUSSION sections have been updated accordingly.

Under RESULTS, page 10, lines 8-24 and page 9 lines 1-16:

“Figure 3 and Supplementary Table 6 detail the results of the primary analyses. Supplementary Table 7 details the effect size of the interactions between revascularisation therapies and the relationship between the exposures of interest and in-hospital outcomes. Amongst patients not receiving IVT, AF only (1.90 (1.83-1.96)), HF only ((1.81 (1.72-1.89)) and AF+HF (2.63 (2.51-2.75)) were associated with increased odds of in-hospital mortality. Amongst patients receiving IVT, AF only (1.43 (1.28-1.58)), HF only (1.35 (1.13-1.60)) and AF+HF (1.72 (1.49-1.99)) were associated with increases in the odds of in-hospital mortality which were significantly lower than the increases recorded amongst patients not undergoing IVT (P value for interaction <0.001). Thus, IVT was associated with 25% decreases in the AF-only and HF-only associated increases in the odds of in-hospital mortality, while a 35% decrease was recorded in AF+HF patients. AF only, HF only and AF+HF were associated with significant increases in the odds of prolonged hospitalisation amongst both the IVT and no IVT groups. The increases in the odds of prolonged hospitalisation associated with AF only and AF+HF, but not HF only, were significantly higher amongst patients undergoing IVT than in those not undergoing IVT (P value for interaction ≤0.001). AF only, HF only and AF+HF were associated with significant increases in the odds of moderate-to-severe disability on discharge amongst both the IVT and no IVT groups. AF only, HF only and AF+HF were associated with significant increases in the odds of all-cause bleeding amongst both the IVT and no IVT groups. The increases in the odds of all-cause bleeding associated with AF only and AF+HF were significantly lower amongst patients undergoing IVT than in those not undergoing IVT (P value for interaction ≤0.001).”
Amongst patients not receiving ET, AF only (1.88 (1.82-1.95)), HF only ((1.79 (1.71-1.88)) and AF+HF (2.58 (2.47-2.70)) were associated with increased odds of in-hospital mortality. Amongst patients receiving ET, AF only (0.75 (0.60-0.93)) was associated with decreased odds of in-hospital mortality. There were no associations between HF only (0.73 (0.49-1.10)) or AF+HF (0.88 (0.64-1.12)) and in-hospital mortality amongst patients undergoing ET. Thus, ET was associated with 60% decreases in the AF-only and HF-only associated increases in the odds of in-hospital mortality, while a 66% decrease was recorded in AF+HF patients. Amongst patients not receiving ET, AF only, HF only and AF+HF were associated with increased odds of prolonged hospitalisation, moderate-to-severe disability on discharge and all-cause bleeding. There were no associations between the exposure groups and prolonged hospitalisation, moderate-to-severe disability on discharge or all-cause bleeding amongst patients undergoing ET.”

Under DISCUSSION, page 12 lines 20-24 and page 13 lines 1-25:

“IVT therapy was associated with significant reductions in the excess odds of in-hospital mortality and all-cause bleeding associated with AF and AF+HFall exposure groups. Nevertheless, higher reductions in excess in-hospital mortality associated with IVT were recorded in patients with AF+HF than in those with either AF only or HF only. IVT was nevertheless associated with an increase in the excess odds of prolonged hospitalisation associated with AF and AF+HF. Post-hoc analyses aimed at further characterising this finding revealed that this may be because IVT was associated with higher odds of bleeding in all AIS patients, but the IVT-associated excess odds of bleeding were significantly higher amongst patients with neither AF nor HF than in those with AF only or AF+HF. Given that prior anticoagulation is a contra-indication to IVT36, this finding may be due to the fact that only AF patients without prior anticoagulant therapy may have been offered IVT, resulting in an overall lower bleeding risk amongst these patients. IVT therapy was associated with significant reductions in the excess odds of all-cause bleeding associated with AF and AF+HF. Our results also show that AIS patients with co-morbid HF undergoing IVT were at lower odds of in-hospital mortality and similar odds of discharge disability and all-cause bleeding compared to their counterparts not undergoing IVT. Out of all the studied outcomes in relation to IVT therapy, discharge disability showed the weakest associations. However, it is important to consider when interpreting these results that we defined discharge disability as a proxy based on discharge destination.
ET was associated with significant reductions in the AF- and AF+HF-associated excess odds of in-hospital mortality, discharge disability and all-cause bleeding. Furthermore, ET was also associated with significant reductions in the HF-associated excess odds of in-hospital mortality and all-cause bleeding. Similarly as with IVT,

	higher reductions in excess in-hospital mortality associated with ET were recorded in patients with AF+HF than in those with either AF only or HF only. Amongst AIS patients undergoing ET, AF was associated with decreased odds of in-hospital mortality whilst there were no other associations between AF, HF or AF+HF and any other pre-specified outcomes. Post-hoc analyses revealed that these findings may be because ET disproportionately increased the odds of adverse outcomes amongst AIS patients with neither AF nor HF, but not amongst those with AF or HF. Having adjusted our analyses by age and co-morbidity profile, it is reasonable to hypothesise that.”

Cover Letter

Professor Paolo G. Camici
Editor-in-Chief
International Journal of Cardiology

Subject: Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure

Dear Professor Camici,

We are pleased to submit an original research article entitled **"Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure"** to be considered for publication in the *International Journal of Cardiology*.

Both atrial fibrillation (AF) and heart failure (HF) are associated not only with increased incidence of acute ischaemic stroke, but also with poor post-ischaemic stroke outcomes. Furthermore, we have previously shown that patients with co-existing AF and HF experience significantly worse post-stroke in-hospital outcomes compared to patients with either AF alone or HF alone, thus suggesting that the associations between the two co-morbidities and poor outcomes are cumulative in the short term. Furthermore, the effects of AF and HF on the outcomes of ischaemic stroke patients undergoing intravenous thrombolysis or endovascular thrombectomy are not fully understood.

In this study, we aimed to answer these questions by analysing all acute ischaemic stroke admissions from the US National Inpatient Sample between 2004 and 2015, yielding a sample representative of more than 4.5 million admissions. We defined the exposure groups by stratifying the sample into 4 mutually exclusive groups: patients with neither AF nor HF, those with AF only, those with HF only or those with both AF and HF. We compared the outcomes between these groups performing further stratifications by whether patients underwent intravenous thrombolysis or endovascular thrombectomy during their hospital admission. We have found that acute ischaemic stroke patients with co-morbid AF and/or HF undergoing intravenous thrombolysis had either better or at least comparable in-hospital outcomes to their counterparts not undergoing thrombolysis. Furthermore, there were no positive associations between AF or HF and adverse in-hospital outcomes amongst AIS patients undergoing ET. We conclude that revascularisation therapies should be considered and offered routinely in acute ischemic stroke patients with these comorbidities unless contra-indicated and that endovascular thrombectomy may be an effective therapeutic strategy to manage the excess risk of adverse short-term outcomes associated with AF and/or HF in acute ischaemic stroke.

We believe that our findings will be of interest to the readership of the *International Journal of Cardiology* and also relevant to researchers, clinicians and the public.

All authors have read and approved the submitted manuscript, the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract. We look forward to hearing from you.

Yours sincerely,

Professor Phyo K Myint (corresponding author); Clinical Chair in Old Age Medicine
For and on behalf of all co-authors

28 August 2020

Professor Paolo G. Camici
Editor-in-Chief
International Journal of Cardiology

Subject: Revision of Manuscript ID IJC_2020_1732_R2

Dear Professor Camici,

We thank the editors for giving us the opportunity to re-submit a revised version of an original article entitled ***"Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure"*** to be considered for publication in the *International Journal of Cardiology***.**

We provide below point-by-point responses to the comments made by the reviewer.

We also attached a tracked version of our manuscript. Given that this is a third revision, we have tracked our changes on a clean version of the manuscript submitted for the second revision.

On behalf of all co-authors, I would like to take the opportunity to thank the Editorial Board for considering our paper and the reviewers for their helpful comments.

We sincerely hope that the revised version will satisfy the reviewers and the editors, and that the revised manuscript will be acceptable in the current form. We look forward to hearing from you.

Yours sincerely,

Professor Phyo K Myint (corresponding author)
Clinical Chair in Old Age Medicine
For and on behalf of all co-authors

We have highlighted the changes in the text, where appropriate, as follows: (additions in blue, deletions in ~~red~~):.

Comments from reviewers:

REVIEWER 5

- This manuscript is a large-scale cohort study of acute ischemic stroke patients. Implication on revascularization (Intravenous thrombolysis or endovascular thrombectomy) should be minimized in the conclusion because of the following reasons.

1) This is not a prospective intervention study, but a observational study

Response: Thank you very much for taking the time to review our manuscript. We appreciate and share the reviewer's concerns about drawing clinical conclusions regarding the use of revascularisation therapies in these patient groups based on an observational study. We have thus modified the conclusions drawn from this study to reflect the fact that while our results drawn from observational data are encouraging, no direct clinical recommendations can be made based on these without further clinical trial data.

Under ABSTRACT, page 2, lines 21-24:

"**Conclusions** –We confirmed the combined and individual impact of co-existing AF or HF on important patient-related outcomes. Revascularisation therapies improve these outcomes significantly in patients with these comorbidities ~~and should be offered routinely unless contra-indicated~~."

Under CONCLUSIONS, page 17, lines 16-24:

"In this study of real-world data, AIS patients with co-morbid AF or HF undergoing IVT had either better or comparable in-hospital adverse outcomes than their counterparts not undergoing IVT. There were no positive associations between AF or HF and adverse in-hospital outcomes amongst AIS patients undergoing ET. Therefore, ~~C~~co-morbid AF and/or HF should not solely represent a criterion against delivering IVT therapy to AIS patients. Furthermore,~~,~~ ~~while~~ ET may be an effective therapeutic strategy to manage the excess risk of adverse short-term outcomes associated with AF and/or HF in AIS. ~~Therefore, revascularisation therapies should be considered and offered routinely in acute ischemic stroke patients with these comorbidities unless contra-indicated.~~"

The study HIGHLIGHTS have also been updated accordingly:

"

- We examined the impact of IVT and ET on stroke outcomes in patients with AF and HF
- Estimates were calculated for all US ischemic stroke admissions between 2004-2015
- AF and HF were associated with significantly worse in-hospital outcomes
- IVT/ET reduced the AF/HF-associated excess odds of adverse in-hospital outcomes
- IVT/ET should be ~~offered routinely~~considered in ischemic stroke patients with AF/HF if not contraindicated.

”

2) The authors did not compare effect sizes of revascularization therapy on outcomes among different patient groups. Therefore, it is unclear at present whether revascularization is more effective in a specific patient group of AF(+)HF(+) compared with AF(-)HF(-).

Response: Thank you for highlighting this issue. We share the reviewer's concern that a direct comparison between the effect sizes of the IVT/ET interaction terms across the different exposure groups is warranted. Such direct comparisons can be performed by comparing the magnitudes of each IVT/ET interaction terms. We have thus added the following supplementary table displaying the odds ratios and 95% confidence intervals of the IVT and ET interaction terms with each one of the three exposure groups:

Supplementary Table 7. Interaction terms between revascularisation therapy (intravenous thrombolysis or endovascular thrombectomy) and the relationship between the exposures of interest and in-hospital outcomes (also see *Supplementary Table 6*).

	AF only	**HF only**	**AF+HF**
		IVT Interaction Term	
In-Hospital Mortality	**0.75 (0.67-0.84)**	**0.75 (0.62-0.89)**	**0.65 (0.56-0.76)**
Los > Median	**1.23 (1.14-1.32)**	1.07 (0.95-1.20)	**1.16 (1.04-1.30)**
Discharge Disability	0.96 (0.89-1.04)	0.92 (0.81-1.05)	0.95 (0.82-1.10)
All-cause Bleeding	**0.87 (0.78-0.97)**	0.89 (0.74-1.07)	**0.75 (0.64-0.88)**
		ET Interaction Term	
In-Hospital Mortality	**0.40 (0.32-0.50)**	**0.41 (0.27-0.61)**	**0.34 (0.25-0.47)**
Los > Median	**0.70 (0.58-0.83)**	0.96 (0.69-1.34)	**0.65 (0.51-0.83)**
Discharge Disability	**0.59 (0.48-0.74)**	0.75 (0.49-1.15)	0.76 (0.52-1.11)
All-cause Bleeding	**0.56 (0.45-0.69)**	**0.54 (0.37-0.78)**	**0.52 (0.39-0.69)**

IVT – Intravenous Thrombolysis, ET – Endovascular Thrombectomy
All regression models were adjusted for age, sex, ethnicity, smoking status, hospital characteristics (bed size, location, teaching status), 29 Elixhauser co-morbidities and other co-morbidities (myocardial infarction, coronary heart disease, other arrhythmias, dyslipidaemia, previous transient ischaemic attack, dementia, shock), previous coronary artery bypass surgery, and family history of cerebrovascular events or ischaemic heart disease.
Statistically significant ($P < 0.01$) results are displayed in **Bold**

Furthermore, the RESULTS and DISCUSSION sections have been updated accordingly.

Under RESULTS, page 10, lines 8-24 and page 9 lines 1-16:

" Figure 3 and Supplementary Table 6 detail the results of the primary analyses. Supplementary Table 7 details the effect size of the interactions between revascularisation therapies and the relationship between the exposures of interest and in-hospital outcomes. Amongst patients not receiving IVT, AF only (1.90 (1.83-1.96)), HF only ((1.81 (1.72-1.89)) and AF+HF (2.63 (2.51-2.75)) were associated with increased odds of in-hospital mortality. Amongst patients receiving IVT, AF only (1.43 (1.28-1.58)), HF only (1.35 (1.13-1.60)) and AF+HF (1.72 (1.49-1.99)) were associated with increases in the odds of in-hospital mortality which were significantly lower than the increases recorded amongst patients not undergoing IVT (*P* value for interaction <0.001). Thus, IVT was associated with 25% decreases in the AF-only and HF-only associated increases in the odds of in-hospital mortality, while a 35% decrease was recorded in AF+HF patients. AF only, HF only and AF+HF were associated with significant increases in the odds of prolonged hospitalisation amongst both the IVT and no IVT groups. The increases in the odds of prolonged hospitalisation associated with AF only and AF+HF, but not HF only, were significantly higher amongst patients undergoing IVT than in those not undergoing IVT (*P* value for interaction ≤0.001). AF only, HF only and AF+HF were associated with significant increases in the odds of moderate-to-severe disability on discharge amongst both the IVT and no IVT groups. AF only, HF only and AF+HF were associated with significant increases in the odds of all-cause bleeding amongst both the IVT and no IVT groups. The increases in the odds of all-cause bleeding associated with AF only and AF+HF were significantly lower amongst patients undergoing IVT than in those not undergoing IVT (*P* value for interaction ≤0.001)."

Amongst patients not receiving ET, AF only (1.88 (1.82-1.95)), HF only ((1.79 (1.71-1.88)) and AF+HF (2.58 (2.47-2.70)) were associated with increased odds of in-hospital mortality. Amongst patients receiving ET, AF only (0.75 (0.60-0.93)) was associated with decreased odds of in-hospital mortality. There were no associations between HF only (0.73 (0.49-1.10)) or AF+HF (0.88 (0.64-1.12)) and in-hospital mortality amongst patients undergoing ET. Thus, ET was associated with 60% decreases in the AF-only and HF-only associated increases in the odds of in-hospital mortality, while a 66% decrease was recorded in AF+HF patients. Amongst patients not receiving ET, AF only, HF only and AF+HF were associated with increased odds of prolonged hospitalisation, moderate-to-severe disability on discharge and all-cause bleeding. There were no associations between the exposure groups and prolonged hospitalisation, moderate-to-severe disability on discharge or all-cause bleeding amongst patients undergoing ET."

Under DISCUSSION, page 12 lines 20-24 and page 13 lines 1-25:

" IVT therapy was associated with significant reductions in the excess odds of in-hospital mortality ~~and all-cause bleeding~~ associated with ~~AF and AF+HF~~all exposure groups. Nevertheless, higher reductions in excess in-hospital mortality associated with IVT were recorded in patients with AF+HF than in those with either AF only or HF only. IVT was ~~nevertheless~~ associated with an increase in the excess odds of prolonged hospitalisation

associated with AF and AF+HF. Post-hoc analyses aimed at further characterising this finding revealed that this may be because IVT was associated with higher odds of bleeding in all AIS patients, but the IVT-associated excess odds of bleeding were significantly higher amongst patients with neither AF nor HF than in those with AF only or AF+HF. Given that prior anticoagulation is a contra-indication to IVT[36], this finding may be due to the fact that only AF patients without prior anticoagulant therapy may have been offered IVT, resulting in an overall lower bleeding risk amongst these patients. IVT therapy was associated with significant reductions in the excess odds of all-cause bleeding associated with AF and AF+HF. Our results also show that AIS patients with co-morbid HF undergoing IVT were ~~at lower odds of in-hospital mortality and~~ similar odds of discharge disability and all-cause bleeding compared to their counterparts not undergoing IVT. Out of all the studied outcomes in relation to IVT therapy, discharge disability showed the weakest associations. However, it is important to consider when interpreting these results that we defined discharge disability as a proxy based on discharge destination.

ET was associated with significant reductions in the AF- and AF+HF-associated excess odds of in-hospital mortality, discharge disability and all-cause bleeding. Furthermore, ET was also associated with significant reductions in the HF-associated excess odds of in-hospital mortality and all-cause bleeding. Similarly as with IVT, higher reductions in excess in-hospital mortality associated with ET were recorded in patients with AF+HF than in those with either AF only or HF only. Amongst AIS patients undergoing ET, AF was associated with decreased odds of in-hospital mortality whilst there were no other associations between AF, HF or AF+HF and any other pre-specified outcomes. Post-hoc analyses revealed that these findings may be because ET disproportionately increased the odds of adverse outcomes amongst AIS patients with neither AF nor HF, but not amongst those with AF or HF. Having adjusted our analyses by age and co-morbidity profile, it is reasonable to hypothesise that."

Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure

Highlights

- We examined the impact of IVT and ET on stroke outcomes in patients with AF and HF
- Estimates were calculated for all US ischemic stroke admissions between 2004-2015
- AF and HF were associated with significantly worse in-hospital outcomes
- IVT/ET reduced the AF/HF-associated excess odds of adverse in-hospital outcomes
- IVT/ET should be ~~offered routinely~~considered in ischemic stroke patients with AF/HF if not contraindicated.

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ABSTRACT

Background – Atrial fibrillation (AF) and heart failure (HF) carry a poor prognosis in acute ischaemic stroke (AIS). The impact of revascularisation therapies on outcomes in these patients is not fully understood.

Methods –National Inpatient Sample (NIS) AIS admissions (January 2004-September 2015) were included (n=4,597,428). Logistic regressions analysed the relationship between exposures (neither AF nor HF-reference, AF-only, HF-only, AF+HF) and outcomes (in-hospital mortality, length-of-stay >median and moderate-to-severe disability on discharge), stratifying by receipt of intravenous thrombolysis (IVT) or endovascular thrombectomy (ET).

Results - 69.2% patients had neither AF nor HF, 16.5% had AF-only, 7.5% had HF-only and 6.7% had AF+HF. 5.04% and 0.72% patients underwent IVT and/or ET, respectively. AF-only and HF-only were each associated with 75-85% increase in the odds of in-hospital mortality. AF+HF was associated with greater than two-fold increase in mortality. Patients with AF-only, HF-only or AF+HF undergoing IVT had better or at least similar in-hospital outcomes compared to their counterparts not undergoing IVT, except for prolonged hospitalisation. Patients undergoing ET with AF-only, HF-only or AF+HF had better (in-hospital mortality, discharge disability, all-cause bleeding) or at least similar (length-of-stay) outcomes to their counterparts not undergoing ET. Compared to AIS patients without AF, AF patients had approximately 50% and more than two-fold increases in the likelihood of receiving IVT or ET, respectively.

Conclusions –We confirmed the combined and individual impact of co-existing AF or HF on important patient-related outcomes. Revascularisation therapies improve these outcomes significantly in patients with these comorbidities ~~and should be offered routinely unless contra-indicated~~.

Keywords: atrial fibrillation, heart failure, cerebrovascular disease, stroke, thrombolysis, thrombectomy;

Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure

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Word count: ~~3884~~4002

Tables 1, Figures 3

Revascularisation Therapies Improve the Outcomes of Ischemic Stroke Patients with Atrial Fibrillation and Heart Failure

Tiberiu A Pana[a,b], MRes; Mohamed O Mohamed[a], MRCP (UK); Allan B Clark[c], PhD; Eoin Fahy[a], MRCP (Ireland); Mamas A Mamas[a], DPhil; Phyo K Myint[a,b,c], MD

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Tables 1, Figures 3

ABSTRACT

Background – Atrial fibrillation (AF) and heart failure (HF) carry a poor prognosis in acute ischaemic stroke (AIS). The impact of revascularisation therapies on outcomes in these patients is not fully understood.

Methods –National Inpatient Sample (NIS) AIS admissions (January 2004-September 2015) were included (n=4,597,428). Logistic regressions analysed the relationship between exposures (neither AF nor HF-reference, AF-only, HF-only, AF+HF) and outcomes (in-hospital mortality, length-of-stay >median and moderate-to-severe disability on discharge), stratifying by receipt of intravenous thrombolysis (IVT) or endovascular thrombectomy (ET).

Results - 69.2% patients had neither AF nor HF, 16.5% had AF-only, 7.5% had HF-only and 6.7% had AF+HF. 5.04% and 0.72% patients underwent IVT and/or ET, respectively. AF-only and HF-only were each associated with 75-85% increase in the odds of in-hospital mortality. AF+HF was associated with greater than two-fold increase in mortality. Patients with AF-only, HF-only or AF+HF undergoing IVT had better or at least similar in-hospital outcomes compared to their counterparts not undergoing IVT, except for prolonged hospitalisation. Patients undergoing ET with AF-only, HF-only or AF+HF had better (in-hospital mortality, discharge disability, all-cause bleeding) or at least similar (length-of-stay) outcomes to their counterparts not undergoing ET. Compared to AIS patients without AF, AF patients had approximately 50% and more than two-fold increases in the likelihood of receiving IVT or ET, respectively.

Conclusions –We confirmed the combined and individual impact of co-existing AF or HF on important patient-related outcomes. Revascularisation therapies improve these outcomes significantly in patients with these comorbidities ~~and should be offered routinely unless contra-indicated~~.

Keywords: atrial fibrillation, heart failure, cerebrovascular disease, stroke, thrombolysis, thrombectomy;

1. Introduction

Atrial fibrillation (AF) and heart failure (HF) are associated with increased incidence of acute ischaemic stroke (AIS)[1,2] and post-AIS adverse outcomes[3-7]. Furthermore, AF and HF frequently co-exist[8] and it is well documented that AIS patients with co-existing AF and HF experience worse in-hospital outcomes than their counterparts with either AF or HF alone[7].

Both intravenous thrombolysis (IVT) and endovascular thrombectomy (ET) have been shown to improve post-AIS mortality and functional outcomes[9,10]. The effect of AF and HF on the outcomes of AIS patients undergoing IVT or ET remains unclear. Previous small-scale observational studies and retrospective analyses of trial data have yielded equivocal results on whether co-morbid AF or HF may be associated with worse[11-15], similar[16-19] or better[20,21] outcomes in AIS patients undergoing IVT. A meta-analysis found that AF was associated with excess mortality, disability and bleeding at 90 days post-discharge amongst AIS patients undergoing IVT[22]. Similarly, no associations between AF[23,24] or HF[25] and worse outcomes after ET were found despite suggestions that cardioembolic stroke may be an independent predictor of adverse outcomes after ET[26]. Finally, no previous study has assessed the association between the co-existent AF and HF and post-AIS outcomes after IVT or ET.

In this study, we aimed to determine whether patients with AF, HF and AF+HF have improved AIS in-hospital outcomes (mortality, length-of-stay, discharge disability and all-cause bleeding) with IVT and ET.

2. Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki (1975) and later amendments. The data that support the findings of this study are available from the corresponding author on reasonable request.

2.1 Data source and inclusion criteria

The National Inpatient Sample (NIS) is a large publicly available database containing >7 million annual hospital admission records. The NIS contains admission records representing a 20% stratified sample of all community hospital admissions in the United States in a given timeframe. Using the provided sampling weights, the NIS data can be used to provide national estimates for the sampling population, representative of ~95% of the US population[27,28]. Prior to undertaking this project, all authors completed the online HCUP Data Use Agreement Training Tool. All authors also read and signed the Data Use Agreement for Nationwide Databases. As the NIS is a publicly available database with no patient identifiable information, no ethical approval was needed. Using data files containing annual admissions between 2004-2015, all records with a primary diagnosis of ischaemic stroke (*International Classification of Disease – ninth edition* (ICD9) codes 433.01, 433.11, 433.21, 433.31, 433.8, 433.91, 434.01, 434.11 and 434.91) were extracted. Only cases admitted between January 2004-September 2015 were included due to a change in co-morbidity coding occurring after September 2015[27].

Figure 1 details the study population. A total of 1,005,810 admission records with a primary diagnosis of ischaemic stroke admitted between January 2004-September 2015 were extracted. After applying the exclusion criteria, a total of 952,368 records were included. Elective admissions were excluded to ensure that only admissions which were triggered by the acute stroke event were included and not follow-up admissions occurring after the acute

stroke event. After the application of sampling weights and the exclusion of strata with single sampling units, the included records were used to provide estimates for the population from which they were sampled: 4,597,428 patients admitted with a primary diagnosis of AIS.

2.2 Definition of exposure, confounders and outcomes

Supplementary Table 1 details the ICD9 codes utilised to extract the variables of interest. Co-morbid conditions (including AF and HF) were also identified using ICD-9 codes and represent diagnoses assigned before or during the index acute ischaemic stroke hospitalisation. AF and HF were defined using all the necessary ICD-9 codes to encompass all the possible subtypes of each disease. The Elixhauser co-morbidities were determined using the HCUP Elixhauser co-morbidity software[29]. The disability outcome was estimated using a previously validated method using the discharge destination as a proxy[30]. All records of patients who died in hospital, those who were discharged against medical advice and those discharged to an unknown destination were excluded from the analyses prior to weighting (n=54,569 (5.73%)), allowing estimates for this particular outcome to be provided for 4,334,370 (95.04%) of AIS patients. 'Routine' discharges were classified as none-or-minimal disability on discharge, whilst discharges to 'home health care', 'short-term hospital' and 'other facilities including intermediate care and skilled nursing home' were classified as moderate-to-severe disability on discharge.

2.3 Statistical Analysis

All analyses were performed using Stata 15.1SE, Stata Statistical Software. A 1% threshold of statistical significance was utilised for all analyses ($P < 0.01$). All analyses were performed according to the Healthcare Cost and Utilisation Project (HCUP) guidelines[31], utilising the provided discharge weights as probability weights and survey data analysis

techniques stratifying by NIS stratum and year of admission[32] in order to account for patient clustering within hospitals and produce US-wide estimates[33,34].

2.3.1 Descriptive Statistics

Patient characteristics were compared across the 4 exposure categories using either the χ^2 test or ANOVA, as appropriate. The yearly prevalence of each exposure category and the yearly rates of IVT and ET therapy were computed. The yearly rates of IVT and ET therapy were also computed for different exposure categories.

2.3.2 Primary Analyses

In order to determine whether patients with AF, HF or AF+HF have improved AIS in-hospital outcomes with IVT and ET, multivariable logistic regressions were performed modelling the association between the exposure groups and outcomes, using the neither AF nor HF group as a reference category and including interaction terms with IVT and ET. The regression models were also stratified based on whether received IVT or ET therapy. The models were adjusted for the covariates listed below.

2.3.3 Secondary and Post-hoc analyses

Multivariable logistic regressions were performed modelling the association between exposure groups and the odds of receiving IVT or ET therapy, using the neither AF nor HF group as a reference category. Furthermore, based on the results of the primary analyses, further post-hoc logistic regression models were performed evaluating the relationship between IVT/ET therapy and outcomes, stratified by exposure groups. The models were adjusted for the covariates listed below.

2.3.4 Adjusting co-variates

All models were adjusted for age, sex, ethnicity, smoking status, hospital characteristics (bed size, location, teaching status), 28 Elixhauser comorbidities (human immunodeficiency virus infection/acquired immune deficiency syndrome, alcohol abuse, anemia (deficiency and blood loss), rheumatoid arthritis/collagen vascular disease, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus (with and without complications), drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid & electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, renal failure, solid tumour (without metastasis), peptic ulcer disease, valvular disease, weight loss) and other co-morbidities (myocardial infarction, coronary heart disease, arrhythmias other than AF, dyslipidaemia, previous transient ischaemic attack, dementia, shock), previous coronary artery bypass surgery, and family history of cerebrovascular events or ischaemic heart disease. The Elixhauser co-morbidities were included as individual co-variates. Adjusting co-variates were selected based on clinical judgement and previous literature[3,5-7].

3. Results

3.1 Descriptive Statistics

Table 1 and Supplementary Table 2 summarise the patient characteristics on admission in brief and in full, respectively. Out of 4,597,428 AIS patients, there were 3,182,285 (69.22%) patients with neither AF nor HF, 761,856 (16.59%) patients with AF only, 346,482 (7.54%) patients with HF only and 305,805 (6.65%) patients with AF+HF. The median (inter-quartile range) age of the included cohort was 73 (61-83) years. The median length-of-stay (LoS) was 4 (2-6) days. There were 52.79% females. Patients with AF only, HF only or AF+HF had more co-morbidities (other than AF or HF) than those with neither AF nor HF. There were 231,606 (5.04%) and 33,173 (0.72%) AIS patients undergoing IVT and ET, respectively. The overall in-hospital mortality was 4.92%, whilst amongst patients

with neither AF nor HF, AF only, HF only and AF+HF the mortality rates were 3.24%, 7.90%, 7.60% and 11.97%, respectively. There were 2,709,450 (62.51%) patients with moderate-to-severe discharge disability. A total of 145,927 (3.17%) patients suffered all-cause bleeding.

Supplementary Table 3 summarises the patient characteristics for the patient sample undergoing IVT. AIS patients undergoing IVT had a median (IQR) age of 71 (59-81) years, median (IQR) LoS 5 (3-7) days and were 49.94% females. A total of 16,084 (6.94%) AIS patients undergoing IVT also underwent ET, which constitutes 48.48% of the population of AIS patients undergoing ET. For AIS patients undergoing IVT, the overall in-hospital mortality rate was 8.45%. There were 139,457 (66.33%) patients discharged with a moderate-to-severe discharge disability. A total of 27284 (11.78%) patients suffered in-hospital bleeding. Supplementary Table 4 summarises the patient characteristics for the patient sample undergoing ET. AIS patients undergoing ET had a median (IQR) age of 69 (58-79) years, median (IQR) LoS 7 (4-11) days and were 49.62% females. For AIS patients undergoing ET, the overall in-hospital mortality rate was 16.66%. There were 22,399 (81.17%) patients discharged with a moderate-to-severe discharge disability. A total of 8896 (26.82%) AIS patients undergoing ET suffered all-cause bleeding.

Figure 2 summarises the estimated yearly prevalence of the exposure groups between 2004-2015. The estimated prevalence of AF without HF increased steadily between 2004 and 2011 from 14.2% to 17.7%, after which it reached a plateau until 2015 at ~17.8%. The estimated prevalence of HF without AF was ~7.3-7.9% throughout 2004-2015. The estimated prevalence of AF+HF was ~6.5% between 2004 and 2010, increasing steadily between 2010 and 2015 to 7.3%. Figure 2 also summarises the estimated yearly rates of IVT and ET between 2004-2015. The IVT rate increased steadily between 2004 (1.65%) and 2015 (8.27%). The ET rate also increased steadily between 2008 (0.55%) and 2015 (2.05%).

Supplementary Figure 1 and Supplementary Table 5 summarise the estimated yearly rates of IVT and ET therapy stratified by the exposure groups. The IVT and ET rates were significantly higher amongst patients with AF only and AF+HF than in patients with HF only or neither AF nor HF throughout the study period.

3.2 Primary Analyses

Figure 3 and Supplementary Table 6 detail the results of the primary analyses. Supplementary Table 7 details the effect size of the interactions between revascularisation therapies and the relationship between the exposures of interest and in-hospital outcomes. Amongst patients not receiving IVT, AF only (1.90 (1.83-1.96)), HF only ((1.81 (1.72-1.89)) and AF+HF (2.63 (2.51-2.75)) were associated with increased odds of in-hospital mortality. Amongst patients receiving IVT, AF only (1.43 (1.28-1.58)), HF only (1.35 (1.13-1.60)) and AF+HF (1.72 (1.49-1.99)) were associated with increases in the odds of in-hospital mortality which were significantly lower than the increases recorded amongst patients not undergoing IVT (*P* value for interaction <0.001). Thus, IVT was associated with 25% decreases in the AF-only and HF-only associated increases in the odds of in-hospital mortality, while a 35% decrease was recorded in AF+HF patients. AF only, HF only and AF+HF were associated with significant increases in the odds of prolonged hospitalisation amongst both the IVT and no IVT groups. The increases in the odds of prolonged hospitalisation associated with AF only and AF+HF, but not HF only, were significantly higher amongst patients undergoing IVT than in those not undergoing IVT (*P* value for interaction ≤0.001). AF only, HF only and AF+HF were associated with significant increases in the odds of moderate-to-severe disability on discharge amongst both the IVT and no IVT groups. AF only, HF only and

AF+HF were associated with significant increases in the odds of all-cause bleeding amongst both the IVT and no IVT groups. The increases in the odds of all-cause bleeding associated with AF only and AF+HF were significantly lower amongst patients undergoing IVT than in those not undergoing IVT (*P* value for interaction ≤0.001).

Amongst patients not receiving ET, AF only (1.88 (1.82-1.95)), HF only ((1.79 (1.71-1.88)) and AF+HF (2.58 (2.47-2.70)) were associated with increased odds of in-hospital mortality. Amongst patients receiving ET, AF only (0.75 (0.60-0.93)) was associated with decreased odds of in-hospital mortality. There were no associations between HF only (0.73 (0.49-1.10)) or AF+HF (0.88 (0.64-1.12)) and in-hospital mortality amongst patients undergoing ET. Thus, ET was associated with 60% decreases in the AF-only and HF-only associated increases in the odds of in-hospital mortality, while a 66% decrease was recorded in AF+HF patients. Amongst patients not receiving ET, AF only, HF only and AF+HF were associated with increased odds of prolonged hospitalisation, moderate-to-severe disability on discharge and all-cause bleeding. There were no associations between the exposure groups and prolonged hospitalisation, moderate-to-severe disability on discharge or all-cause bleeding amongst patients undergoing ET.

3.3 Secondary and Post-hoc analyses

Supplementary Table 8~~7~~ details the associations between exposure groups and the odds of receiving IVT or ET. Compared to patients with neither AF nor HF, patients with AF only (Odds Ratio (99% CI) = 1.43 (1.37-1.49)), HF only (1.13 (1.06-1.20)) and AF+HF (1.38 (1.30-1.48)) were more likely to receive IVT. Similarly, compared to patients with neither AF nor HF, those with AF only (2.48 (2.26-2.73)), HF only (1.28 (1.11-1.48)) and AF+HF (2.55 (2.25-2.90)) were more likely to receive ET. Supplementary Table 9~~8~~ details the results of the post-hoc analyses. Both IVT and ET were associated with higher increases in the odds

of in-hospital mortality amongst patients with neither AF nor HF than in those with AF only, HF only or AF+HF. IVT was associated with higher increases in the odds of all-cause bleeding amongst patients with neither AF nor HF, AF only and HF only than in those with AF+HF. ET was associated with a higher increase in the odds of all-cause bleeding amongst patients with neither AF nor HF than in those with AF only, HF only or AF+HF.

4. Discussion

In this analysis of a sample representative of over 4.5 million AIS admissions, we have found that co-existent AF and HF were associated with more than two-fold increased odds of in-hospital mortality, whilst AF only and HF only were each associated with 75-85% increases, suggesting that the excess odds associated with either AF or HF in isolation may be cumulative when the two co-exist. Similar relationships were delineated between the exposure groups and the excess odds of prolonged hospitalisation and moderate-to-severe disability on discharge. Nevertheless, the same effect was not observed for the all-cause bleeding outcome: AF only and AF+HF were associated with ~80-90% increase in the odds of all-cause bleeding, while HF only was only associated with a 33% increase. This is likely reflective of the fact that AF patients are more likely to receive anticoagulant therapy than patients in sinus rhythm[35].

IVT therapy was associated with significant reductions in the excess odds of in-hospital mortality ~~and all-cause bleeding~~ associated with ~~AF and AF+HF~~all exposure groups. Nevertheless, higher reductions in excess in-hospital mortality associated with IVT were recorded in patients with AF+HF than in those with either AF only or HF only. IVT was ~~nevertheless~~ associated with an increase in the excess odds of prolonged hospitalisation

associated with AF and AF+HF. Post-hoc analyses aimed at further characterising this finding revealed that this may be because IVT was associated with higher odds of bleeding in all AIS patients, but the IVT-associated excess odds of bleeding were significantly higher amongst patients with neither AF nor HF than in those with AF only or AF+HF. Given that prior anticoagulation is a contra-indication to IVT[36], this finding may be due to the fact that only AF patients without prior anticoagulant therapy may have been offered IVT, resulting in an overall lower bleeding risk amongst these patients. IVT therapy was associated with significant reductions in the excess odds of all-cause bleeding associated with AF and AF+HF. Our results also show that AIS patients with co-morbid HF undergoing IVT were ~~at lower odds of in-hospital mortality and~~ similar odds of discharge disability and all-cause bleeding compared to their counterparts not undergoing IVT. Out of all the studied outcomes in relation to IVT therapy, discharge disability showed the weakest associations. However, it is important to consider when interpreting these results that we defined discharge disability as a proxy based on discharge destination.

ET was associated with significant reductions in the AF- and AF+HF-associated excess odds of in-hospital mortality, discharge disability and all-cause bleeding. Furthermore, ET was also associated with significant reductions in the HF-associated excess odds of in-hospital mortality and all-cause bleeding. Similarly as with IVT, higher reductions in excess in-hospital mortality associated with ET were recorded in patients with AF+HF than in those with either AF only or HF only. Amongst AIS patients undergoing ET, AF was associated with decreased odds of in-hospital mortality whilst there were no other associations between AF, HF or AF+HF and any other pre-specified outcomes. Post-hoc analyses revealed that these findings may be because ET disproportionately increased the odds of adverse outcomes amongst AIS patients with neither AF nor HF, but not amongst those with AF or HF. Having adjusted our analyses by age and co-morbidity profile, it is reasonable to hypothesise that

factors such the stroke subtype or stroke pre-functional status may explain these findings. Thus, these differences may be attributable to previous findings that ET may be more effective at achieving reperfusion and subsequently better post-stroke outcomes in cardioembolic stroke subtypes[37], which tend to occur more commonly amongst patients with co-morbid AF or HF[38]. Furthermore, current AHA/ASA guidelines recommend that only patients with an excellent pre-stroke functional status (mRS $\leq$ 1) should be offered ET therapy[36], resulting in the selection of only those patients with lower severity of cardiac co-morbidities, which could partly explain the lack of association between AF or HF and any adverse outcomes amongst AIS patients undergoing ET.

Our secondary analyses showed that AIS patients with co-morbid AF, regardless of whether HF co-existed, were 40% more likely to receive IVT therapy and more than twice as likely to receive ET therapy in hospital. Yearly analyses also revealed that these patterns remained constant amid the increasing uptake of IVT and ET during AIS admissions and an increasing prevalence of AF between 2004 and 2015. This highlights the fact that patients with co-morbid AF or HF were more likely to receive evidence-based reperfusion therapy under current clinical practice since the widespread adoption of IVT and ET for emergency AIS management in the United States. It could be that the association between co-morbid AF and ET therapy for AIS may be at least partly driven by the fact that AF patients are more likely to suffer large artery occlusion strokes[39] and thus more likely candidates for ET than patients without AF.

Previous studies assessing revascularisation strategies amongst AIS patients with AF or HF have reached equivocal results. A meta-analysis showed that AF was associated with adverse post-AIS outcomes amongst patients receiving IVT: there was a significant association only with increased 90-day mortality and stroke-related disability, but not in-hospital mortality[22]. Small-scale observational studies have also found that AF was associated

with increased 90-day stroke-related disability and symptomatic intracranial haemorrhage rates amongst AIS patients undergoing IVT[12,13]. Several other observational studies have nevertheless failed to show the same relationships amongst these patients[16,17,20,21]. A retrospective analysis of pooled clinical trial data including more than 5,000 patients concluded that whilst HF was associated with adverse outcomes in patients with AIS undergoing IVT, those patients had nevertheless significantly better outcomes compared to AIS patients with co-morbid HF who did not undergo IVT[15]. It has also been previously found that ET for large artery occlusion stroke did not improve the outcomes of patients with co-morbid AF[23], whilst another study has found that HF may not be associated with excess mortality or disability after ET for large artery occlusion AIS[25].

Our findings may thus provide more clarity regarding the relationship between recanalization strategies in ischaemic stroke and these common co-morbid conditions. The several strengths of our study, such as the large sample size representative of all AIS patients admitted to US hospitals, the wide range of confounders included as adjusting factors in all analyses as well as considering patients with co-existent AF and HF as a separate group, allow the derivation of several clinical implications. Overall, patients with AF or HF undergoing IVT had either better or at least similar in-hospital outcomes compared to their counterparts not receiving IVT, suggesting that solely co-morbid AF and/or HF should not represent a discriminating factor in the decision of whether emergency IVT should be administered to AIS patients. Furthermore, our results pertaining to ET therapy are particularly encouraging and complement previous findings suggesting that ET therapy is efficacious and safe amongst AIS patients with co-morbid AF[23] or HF[25].

We acknowledge certain limitations. Given the nature of the National Inpatient Sample, the ascertainment of exposure groups, co-morbidities, procedures and the all-cause bleeding outcome was based on ICD-9 codes. Given that AF and HF were also ascertained

using ICD-9 codes, these were not validated against clinical data due to lack of this information. It is thus likely that some asymptomatic episodes of paroxysmal AF may not have been captured in the absence of continuous cardiac monitoring in at-risk patients. Nevertheless, our study reflects real-world clinical practice in which continuous cardiac monitoring is not routinely performed with the exception patients with cryptogenic stroke or with pacemakers/implantable cardioverter/defibrillators[40]. Our data also lacked stroke severity measures such as the National Institute of Health Stroke Scale (NIHSS) or the pre- and post-stroke modified Rankin Scale (mRS). Thus, we were unable to perform analyses evaluating outcomes of stroke severity. Nevertheless, we used the patient discharge destination (discharges to 'home health care', 'short-term hospital' and 'other facilities including intermediate care and skilled nursing home') as a proxy for moderate-to-severity disability on discharge in our analyses, which has been previously validated[30]. This measure has been estimated to yield a positive predictive value of 90% of an mRS score of 2-6 at 3 months post-stroke[30]. Furthermore, in the absence of stroke severity data, we were also unable to fully adjust for selection bias in assigning IVT/ET treatment, which may be driven by differences in stroke severity as well as patient demographics and comorbidities between treatment groups. Due to the fact that the application of propensity score matching analyses is yet unclear in the context of complex survey design[41], we have chosen not to perform propensity score matching and we were thus unable to ensure that the treated and untreated groups were balanced in terms of measured confounders. Nevertheless, given our large sample size and number of events per covariate, we deemed traditional covariate adjustment an appropriate alternative[42]. Thus, having adjusted our logistic regression analyses for age, sex, ethnicity and a wide range of co-morbid conditions it is likely that these adjustments partly accounted for such biases. However, residual confounding cannot be eliminated given the non-randomised study design and our results need to be interpreted considering this

limitation. Due to unavailable data, we were unable to account for the time from stroke onset to receipt of revascularisation therapy in our analyses. Nevertheless, according to current guidelines, only patients presenting within 4.5h and 6h of stroke onset are eligible to receive intravenous thrombolysis or endovascular thrombectomy, respectively[36]. Therefore, it is likely that the time from stroke onset may have little influence on the overall patient-related outcomes to the extent to which clinical guidelines guiding the timing of revascularisation therapy were followed. Our study lacks post-discharge follow-up data, which did not allow the analysis of long-term outcomes. Finally, our analyses only included admissions up to September 2015 and it should be noted that ET has only emerged as an evidence-based emergency therapy for AIS in 2015[43]. However, this is unlikely to impact the reliability of our analysis assessing the relationship between exposure groups and AIS outcomes in patients receiving ET. Nevertheless, our findings pertaining to ET therapy should also be confirmed in future research on data including more AIS cases admitted after 2015.

5. Conclusions

In this study of real-world data, AIS patients with co-morbid AF or HF undergoing IVT had either better or comparable in-hospital adverse outcomes than their counterparts not undergoing IVT. There were no positive associations between AF or HF and adverse in-hospital outcomes amongst AIS patients undergoing ET. Therefore, ~~C~~co-morbid AF and/or HF should not solely represent a criterion against delivering IVT therapy to AIS patients. Furthermore,~~,~~ ~~while~~ ET may be an effective therapeutic strategy to manage the excess risk of adverse short-term outcomes associated with AF and/or HF in AIS. ~~Therefore, revascularisation therapies should be considered and offered routinely in acute ischemic stroke patients with these comorbidities unless contra-indicated.~~

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8. Disclosures

None.

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Tables

Table 1. Descriptive statistics of the entire included sample. Further descriptive statistics are detailed in Supplementary Table 2.

	No AF/No HF	AF only	HF only	AF and HF	Total	*P* value
N	3182285	762856	346482	305805	4597428	
			PATIENT CHARACTERISTICS			
Age	69.00 (58.00-80.00)	81.00 (73.00-87.00)	75.00 (63.00-84.00)	82.00 (75.00-88.00)	73.00 (61.00-83.00)	< 0.001
Length of stay (days)	3.00 (2.00-6.00)	4.00 (3.00-7.00)	5.00 (3.00-7.00)	5.00 (3.00-8.00)	4.00 (2.00-6.00)	< 0.001
Sex (Female)	1615220 (50.76)	443521 (58.14)	185520 (53.54)	182591 (59.71)	2426852 (52.79)	< 0.001
Ethnicity						< 0.001
White	1833364 (57.61)	536844 (70.37)	187891 (54.23)	208072 (68.04)	2766172 (60.17)	
Black	497102 (15.62)	51952 (6.81)	71704 (20.69)	29959 (9.80)	650717 (14.15)	
Hispanic	222686 (7.00)	36451 (4.78)	21220 (6.12)	14602 (4.77)	294958 (6.42)	
Asian or Pacific Islander	75368 (2.37)	18604 (2.44)	5585 (1.61)	5314 (1.74)	104871 (2.28)	
Native American	13755 (0.43)	1951 (0.26)	1718 (0.50)	854 (0.28)	18278 (0.40)	
Other	71013 (2.23)	14441 (1.89)	6997 (2.02)	5754 (1.88)	98205 (2.14)	
Missing	468997 (14.74)	102613 (13.45)	51367 (14.83)	41251 (13.49)	664227 (14.45)	
			ELIXHAUSER CO-MORBIDITIES			
HIV/AIDS	7545 (0.24)	283 (0.04)	608 (0.18)	101 (0.03)	8537 (0.19)	< 0.001
Alcohol Abuse	144140 (4.53)	19314 (2.53)	10850 (3.13)	6668 (2.18)	180972 (3.94)	< 0.001
Deficiency anaemia	323057 (10.15)	90127 (11.81)	61276 (17.69)	52686 (17.23)	527145 (11.47)	< 0.001
Rheumatoid Arthritis/Collagen Vascular Disease	75732 (2.38)	18789 (2.46)	8543 (2.47)	7591 (2.48)	110655 (2.41)	0.1
Chronic blood loss anaemia	11675 (0.37)	3868 (0.51)	2312 (0.67)	2478 (0.81)	20333 (0.44)	< 0.001
Chronic Pulmonary Disease	419898 (13.19)	106216 (13.92)	85012 (24.54)	71514 (23.39)	682640 (14.85)	< 0.001

Coagulopathy	77853 (2.45)	25881 (3.39)	12741 (3.68)	13354 (4.37)	129830 (2.82)	< 0.001
Depression	310547 (9.76)	62214 (8.16)	33835 (9.77)	25238 (8.25)	431833 (9.39)	< 0.001
Diabetes Mellitus, Uncomplicated	921666 (28.96)	180367 (23.64)	118374 (34.16)	83378 (27.27)	1303785 (28.36)	< 0.001
Diabetes Mellitus, Chronic Complications	185401 (5.83)	28850 (3.78)	38537 (11.12)	18051 (5.90)	270839 (5.89)	< 0.001
Drug abuse	87892 (2.76)	4206 (0.55)	8925 (2.58)	2169 (0.71)	103192 (2.24)	< 0.001
Hypertension	2524436 (79.33)	616107 (80.76)	280859 (81.06)	237404 (77.63)	3658807 (79.58)	< 0.001
Hypothyroidism	352723 (11.08)	125783 (16.49)	45538 (13.14)	53222 (17.40)	577267 (12.56)	< 0.001
Liver Disease	35698 (1.12)	6035 (0.79)	4702 (1.36)	3387 (1.11)	49822 (1.08)	< 0.001
Lymphoma	15223 (0.48)	4158 (0.55)	2103 (0.61)	1992 (0.65)	23476 (0.51)	0.3
Fluid and Electrolyte Disorders	580279 (18.23)	166351 (21.81)	91010 (26.27)	84336 (27.58)	921976 (20.05)	< 0.001
Metastatic Cancer	48412 (1.52)	9277 (1.22)	4151 (1.20)	2771 (0.91)	64611 (1.41)	< 0.001
Other Neurological Disorders	13016 (0.41)	4446 (0.58)	3031 (0.87)	2408 (0.79)	22901 (0.50)	< 0.001
Obesity	269379 (8.46)	45743 (6.00)	37222 (10.74)	22283 (7.29)	374627 (8.15)	< 0.001
Paralysis	103312 (3.25)	47289 (6.20)	15487 (4.47)	19174 (6.27)	185261 (4.03)	< 0.001
Peripheral Vascular Disease	266993 (8.39)	65072 (8.53)	41089 (11.86)	32705 (10.69)	405859 (8.83)	< 0.001
Psychosis	104710 (3.29)	17108 (2.24)	11523 (3.33)	7310 (2.39)	140651 (3.06)	< 0.001
Pulmonary Circulation Disorders	47601 (1.50)	34644 (4.54)	20056 (5.79)	30798 (10.07)	133099 (2.90)	< 0.001
Renal Failure	306169 (9.62)	89366 (11.71)	90198 (26.03)	69413 (22.70)	555147 (12.08)	< 0.001
Solid Tumour (without metastasis)	51734 (1.63)	14810 (1.94)	5659 (1.63)	5487 (1.79)	77690 (1.69)	< 0.001
Peptic Ulcer Disease (excluding bleeding)	849 (0.03)	303 (0.04)	129 (0.04)	131 (0.04)	1411 (0.03)	< 0.001
Valvular Disease	226197 (7.11)	118171 (15.49)	50235 (14.50)	70312 (22.99)	464915 (10.11)	< 0.001
			PROCEDURES			
Thrombolysis	138647 (4.36)	55253 (7.24)	17012 (4.91)	20694 (6.77)	231606 (5.04)	< 0.001

Echocardiography	425188 (13.36)	75225 (9.86)	39687 (11.45)	26467 (8.65)	566567 (12.32)	< 0.001
Thrombectomy	15580 (0.49)	10826 (1.42)	2376 (0.69)	4390 (1.44)	33173 (0.72)	< 0.001
			OUTCOMES			
In-Hospital Mortality	103173 (3.24)	60251 (7.90)	26319 (7.60)	36606 (11.97)	226349 (4.92)	< 0.001
Los > Median	1116073 (35.07)	369734 (48.47)	175472 (50.64)	172516 (56.41)	1833795 (39.89)	< 0.001
Discharge Disability	1737314 (56.97)	520104 (74.37)	230580 (72.57)	221452 (82.68)	2709450 (62.51)	< 0.001
All-cause Bleeding	96567 (3.03)	48954 (6.42)	17094 (4.93)	21538 (7.04)	184153 (4.01)	< 0.001

Figures

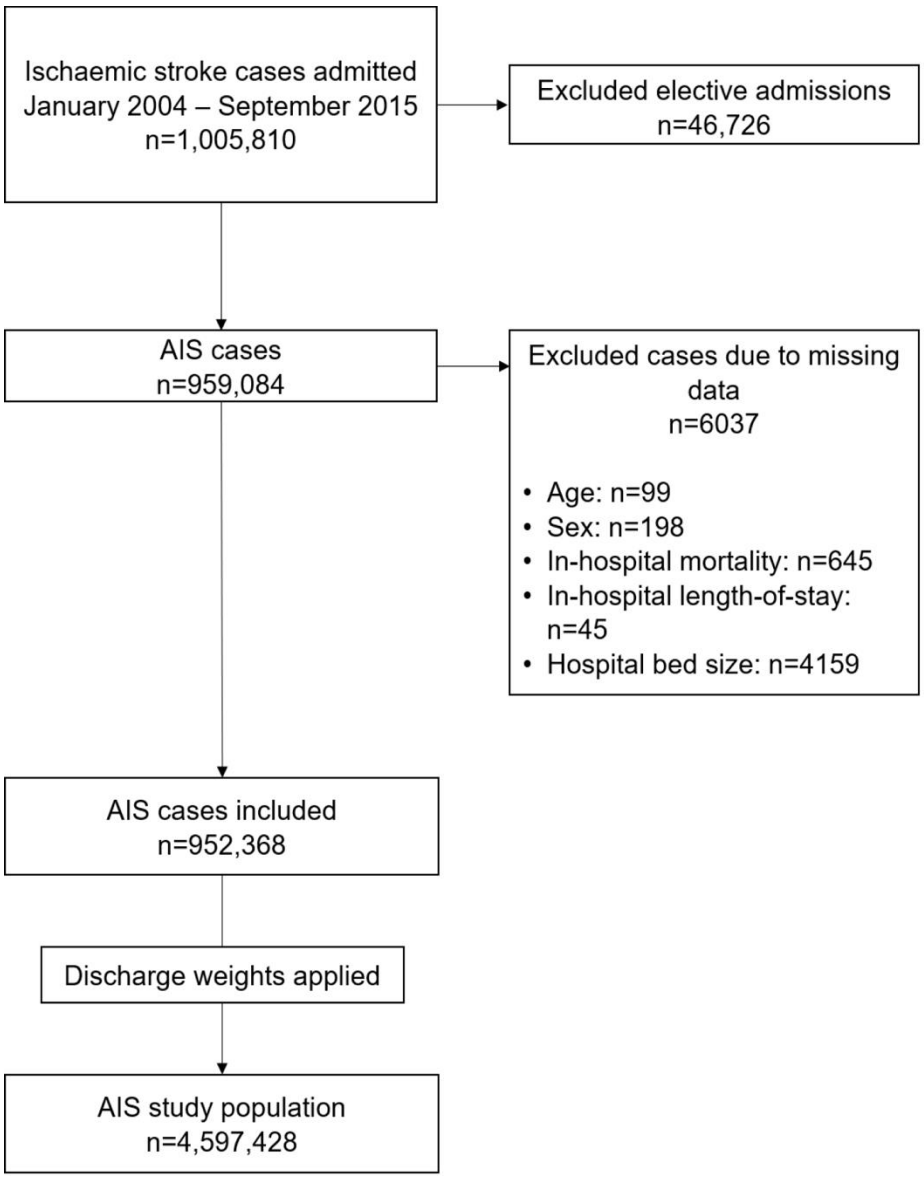

Figure 1. Patient Population Flowchart

AIS – Acute Ischaemic Stroke

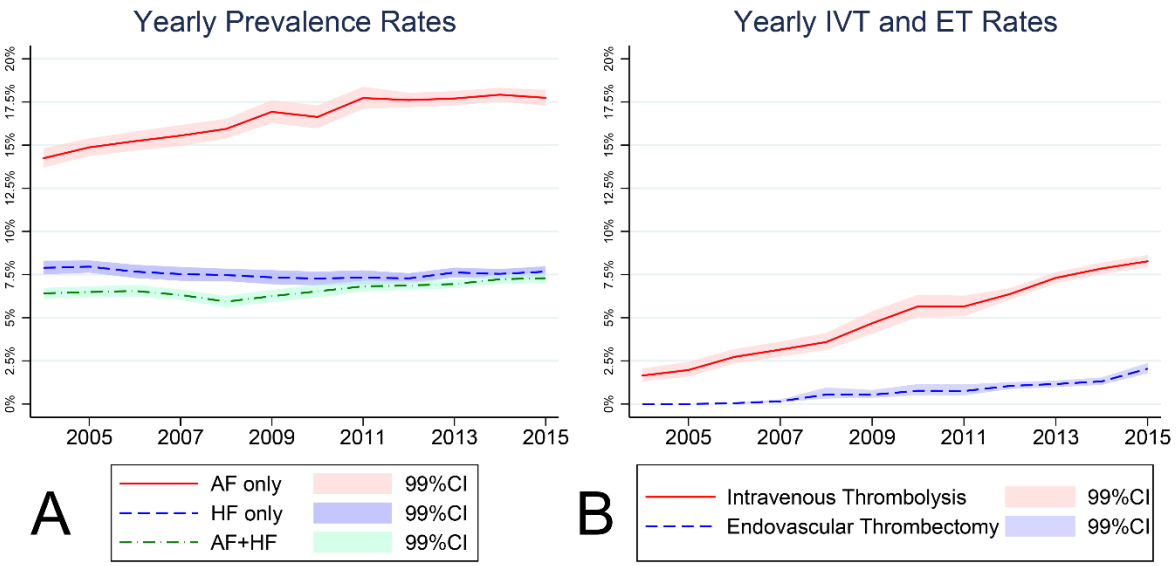

Figure 2. A: Yearly prevalence (2004-2015) of AF, HF and AF+HF amongst AIS patients in the National Inpatient Sample. B: Yearly rates (2004-2015) of intravenous thrombolysis and endovascular thrombectomy during acute ischaemic stroke admissions in the National Inpatient Sample.

AF – atrial fibrillation, HF – heart failure, IVT – intravenous thrombolysis, ET – endovascular thrombectomy

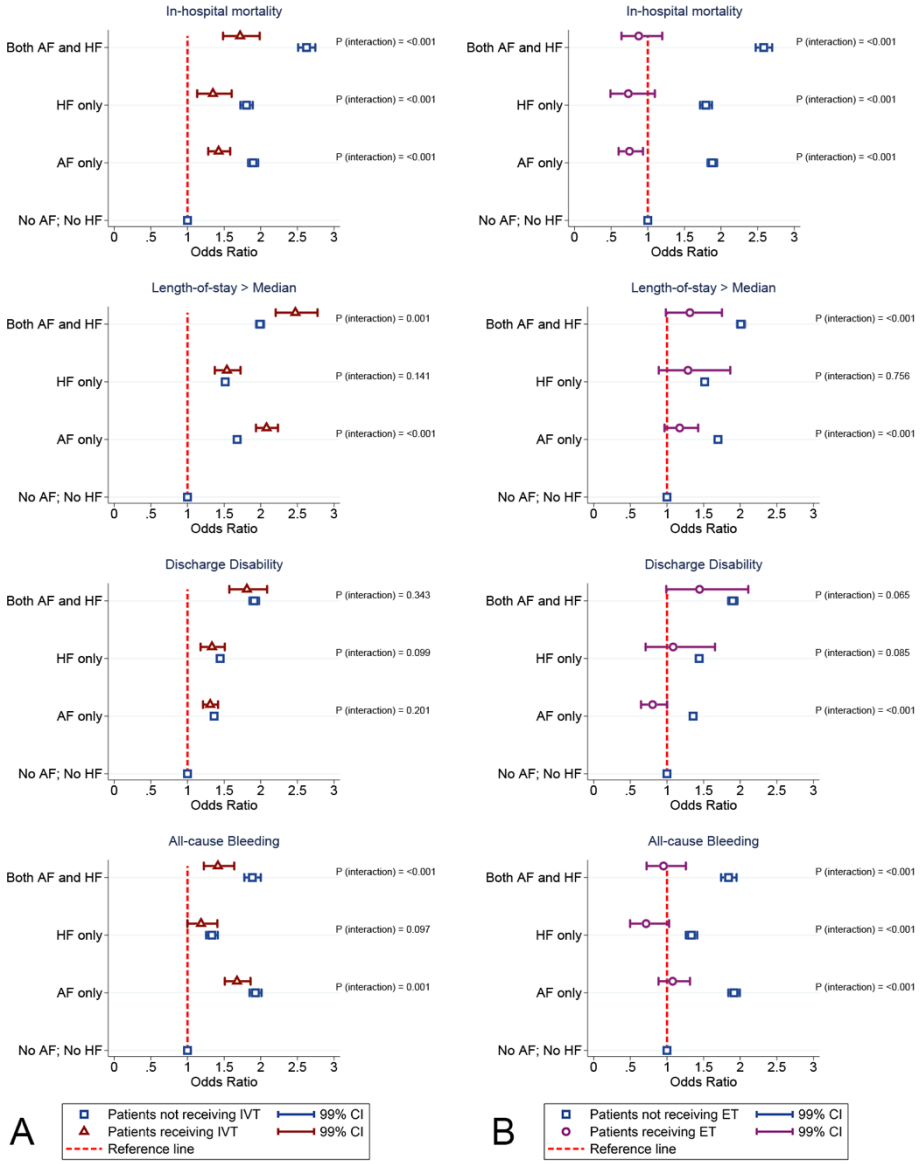

Figure 3. Results of the logistic regressions modelling the associations between co-morbidity status (no AF and no HF; AF only; HF only; AF+HF) and in-hospital outcomes amongst all AIS patients, stratified by whether patients received IVT (A) or ET (B) therapy. The odds ratios are displayed alongside the *P* values corresponding to the interaction term between IVT/ET and co-morbidity status. The no AF and no HF group was used as reference. All models were adjusted for age, sex, ethnicity, smoking status, hospital characteristics (bed size, location, teaching status), 28 Elixhauser co-morbidities and other co-morbidities (myocardial infarction, coronary heart disease, other arrhythmias, dyslipidaemia, previous transient ischaemic attack, dementia, shock), previous coronary artery bypass surgery, and family history of cerebrovascular events or ischaemic heart disease.

AF – atrial fibrillation, HF – heart failure, IVT – intravenous thrombolysis, ET – endovascular thrombectomy

Figure 1. Patient Population Flowchart

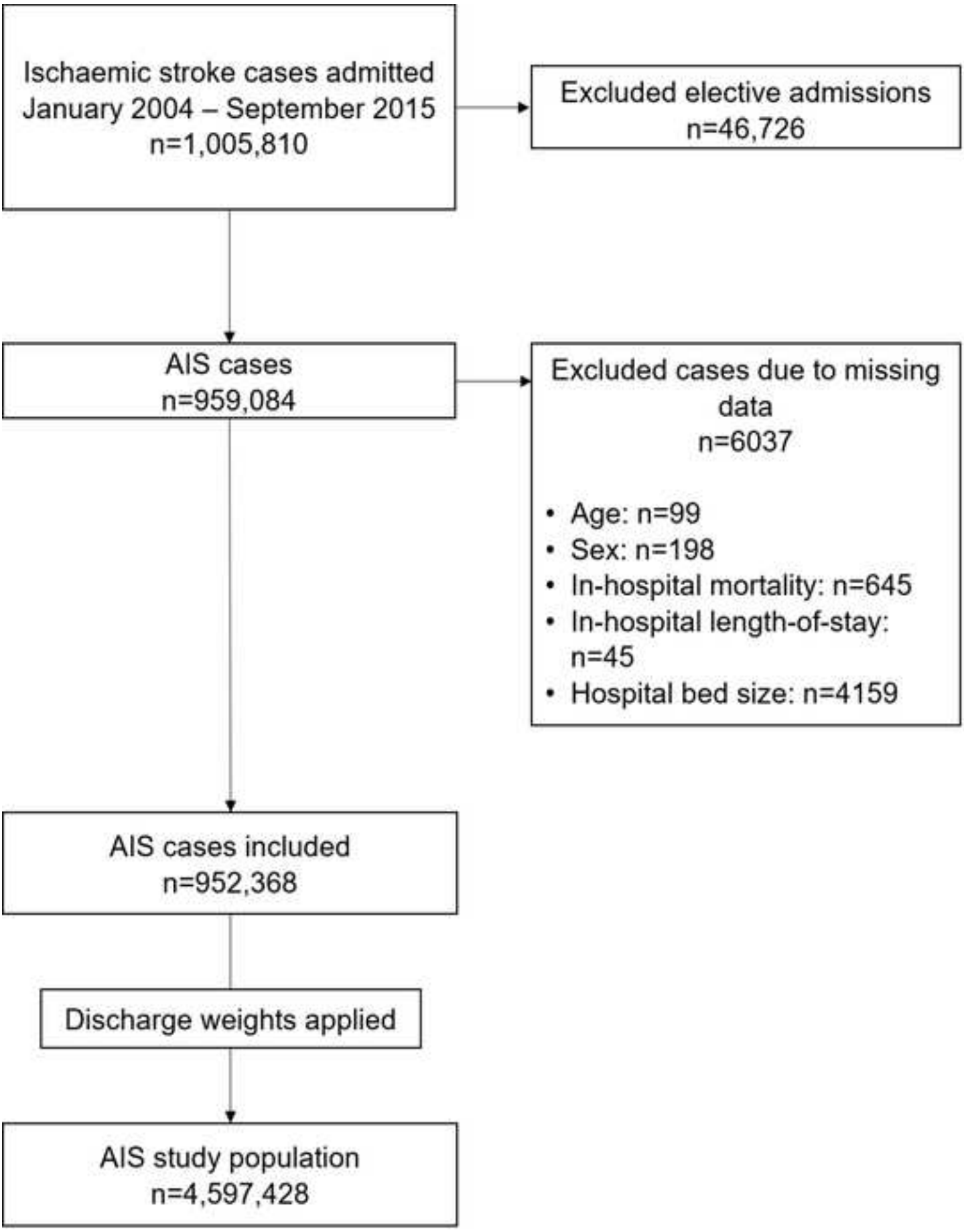

Figure 2. A: Yearly prevalence (2004-2015) of AF, HF and AF+HF amongst AIS patients in the National Inpatient Sample. B: Yearly rates (2004-2015) of intravenous

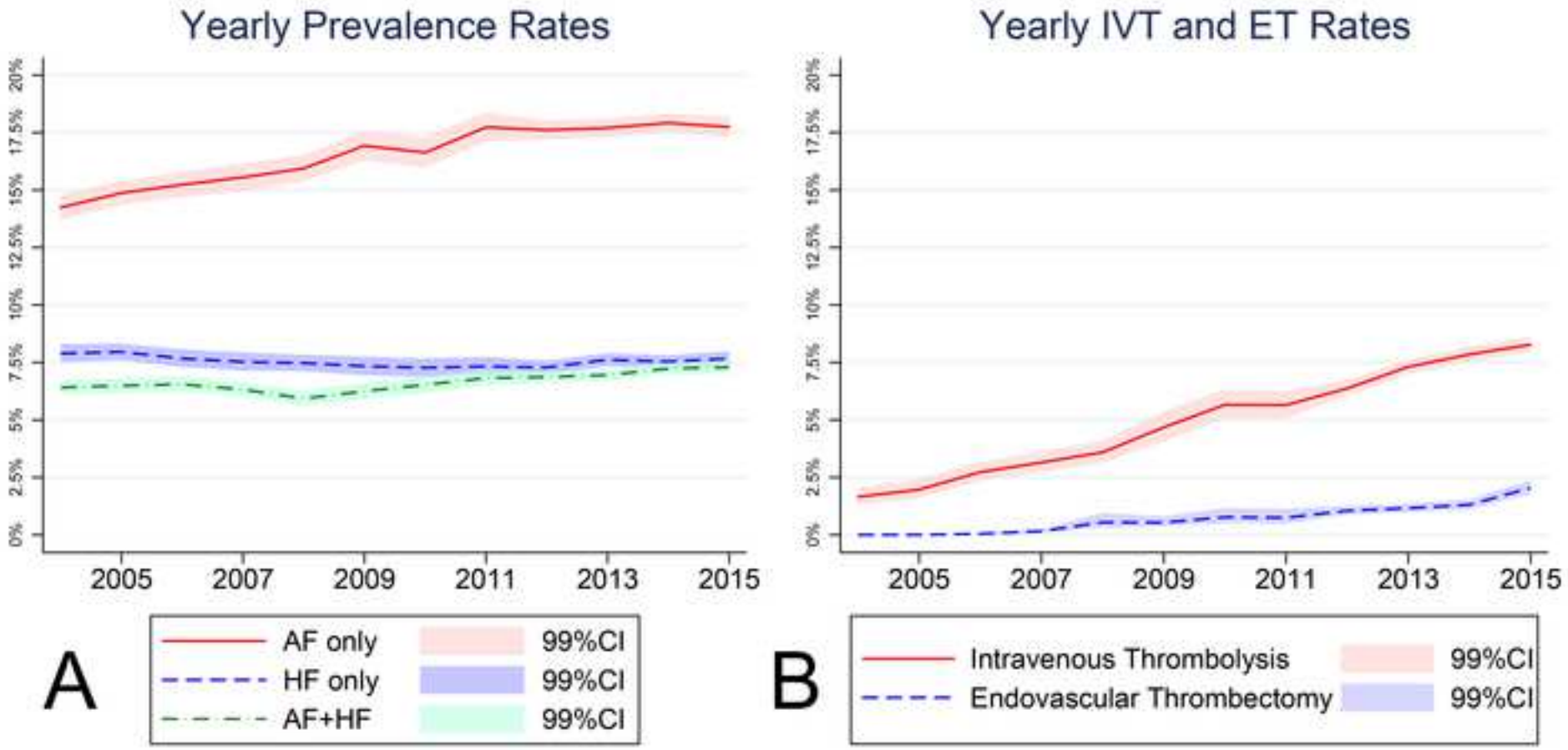

Figure 3.

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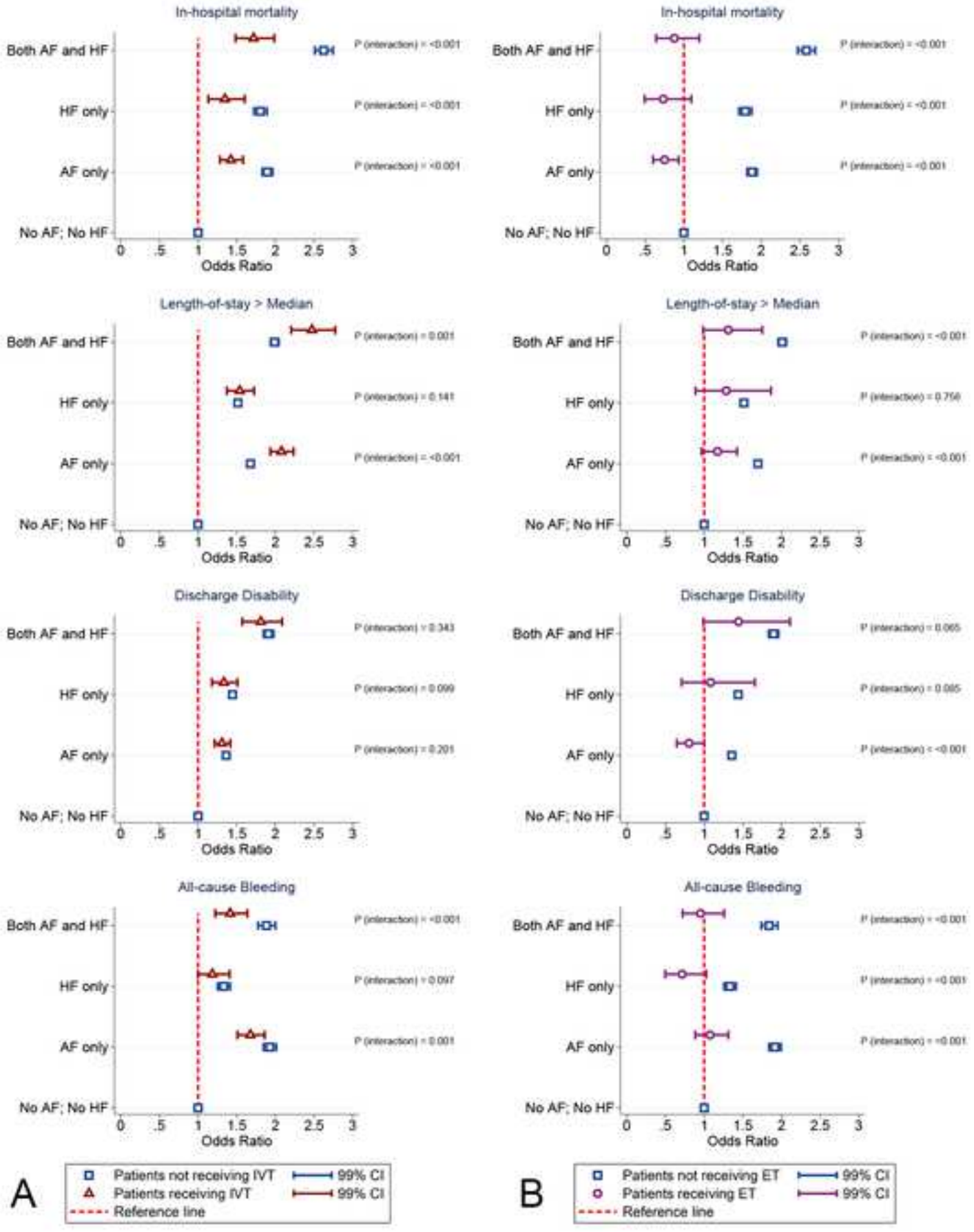

Table 1- Revised with tracked changes

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Table

Table 1.docx

Tiberiu Pana: Conceptualization, Methodology, Statistical Analysis, Writing – Original draft preparation; **Mohamed Mohamed:** Supervision, Writing- Reviewing and Editing**; Allan Clark**: Supervision, Statistical Analysis, Writing- Reviewing and Editing; **Eoin Fahy:** Writing- Reviewing and Editing; **Mamas Mamas**: Conceptualization, Methodology, Writing- Reviewing and Editing; **Phyo Myint:** Conceptualization, Methodology, Supervision, Writing – Original draft preparation.

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List of all Authors: Tiberiu A Pana; Mohamed O Mohamed; Allan B Clark; Eoin Fahy; Mamas A Mamas; Phyo K Myint;

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology.*

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.