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Suboptimal adherence to medical therapy in patients undergoing lower limb angioplasty in Singapore

Dear Editor,

Chronic limb-threatening ischaemia (CLTI) is the advanced stage of peripheral arterial disease (PAD) and patients with this condition face a very high risk of major adverse cardiovascular events and mortality. Several guidelines strongly recommend evidence-based medical therapy (EBMT) to reduce cardiovascular risk.[1-3] Specifically, all CLTI patients should be treated with an antiplatelet agent, moderate- to high-intensity statin therapy, anti-hypertensive therapy to control blood pressure, and anti-diabetic therapy to achieve haemoglobin A1c of <7%.[1] Despite these guidelines, adherence to EBMT is highly variable and Asian data are lacking.[4-6] The aim of this study was to understand the usage of EBMT in CLTI patients.

This was a retrospective cohort study of patients with PAD undergoing lower limb angioplasty at the Singapore General Hospital (SGH) between May 2018 and December 2019. This study was reviewed and approved by the SingHealth Institutional Review Board and written informed consent was obtained from all patients. We extracted demographic and clinical data from the SingHealth Electronic Health Intelligence System,[7] supplemented by manual curation to capture missing comorbidities and dispensing records of the drugs of interest in other SingHealth institutions.

We calculated adherence measures for the 4 classes of drugs recommended in the guidelines: statins, antiplatelets, anti-hypertensives and anti-diabetics. The follow-up period included the baseline (1-year period before angioplasty) and observation window (hospital discharge to 1-year post-discharge or death, whichever was earlier). EBMT use at admission was defined as an overlap of treatment episodes with a 90-day allowable gap with the date of admission. As discharge prescriptions are expected to be given on the discharge date, the overlap of the 0-day gap treatment episode with discharge date was used to avoid overestimations of carry-overs from prescriptions given before and during admission. The level of EBMT adherence post-discharge was measured by the proportion of days covered (PDC) over a 1-year period or until death of the patient, whichever was earlier.

Association between EBMT use at discharge and 1-year post-discharge PDC ≥0.80 was analysed using logistic regression. Associations between EBMT use at discharge and clinical outcomes were analysed using competing risks analyses (angioplasty/minor amputation and major amputation) with death as the competing risk or survival analyses (amputation-free survival [AFS] and overall survival) as appropriate. All analyses were conducted using R version 3.5.1.[8] The AdhereR package version 0.8.1 (CRAN, The Comprehensive R Archive Network) was used to calculate adherence measures.[9]

A total of 722 patients with complete data and discharged alive were included in the analysis. The mean age was 70.3 years (standard deviation=11.0) and 61.1% were male. The prevalence of hypertension, hyperlipidaemia and diabetes was 81.4%, 74.9% and 76.3%, respectively.

The levels of use of the 4 drug classes at admission and discharge are shown in Fig. 1. Of those who received antiplatelets at discharge, 307 (46.4%) received monotherapy, with the majority on aspirin (n=231, 75.2%) and clopidogrel (n=75, 24.4%). Only 1 patient received ticagrelor. Of the patients on antiplatelets, 354 (53.6%) were on dual-antiplatelets; the most common combination was aspirin/clopidogrel (n=344, 97.2%), followed by aspirin/ticagrelor (n=7, 2.0%) and aspirin/dipyridamole (n=3, 0.8%).

The numbers of patients who achieved post-discharge PDC≥0.80 for statins, antiplatelets, anti-hypertensives and anti-diabetics were 317 (43.9%), 373 (51.7%), 362 (50.1%) and 288 (39.9%), respectively. The likelihood for achieving PDC≥0.80 was significantly increased with the use of these drugs at discharge: statins (odds ratio [OR] 9.53, 95% confidence interval [CI] 5.88–16.25), antiplatelets (OR 14.07, 95% CI 6.12–40.73), anti-hypertensives (OR 17.78, 95% CI 8.31–46.22), and anti-diabetics (OR 43.66, 95% CI 20.74–112.39).

Patients who received statins and antiplatelets at discharge were more likely to have a subsequent angioplasty or minor amputation within 1-year post-discharge, compared to patients who did not receive these (32.0% versus 22.1%, *P*=0.027 and 30.7% vs 18.0%, *P*=0.014, respectively). Patients who received anti-diabetics at discharge compared to those who did not, were more likely to have a subsequent angioplasty or minor amputation (33.1% vs 21.4%, $P=4.55 \times 10^{-5}$) and major amputation (11.6% vs 7.4%, *P*=0.012), as well as lower AFS (75.2% vs 77.2%, *P*=0.030) and overall survival (83.0% vs 83.3%,

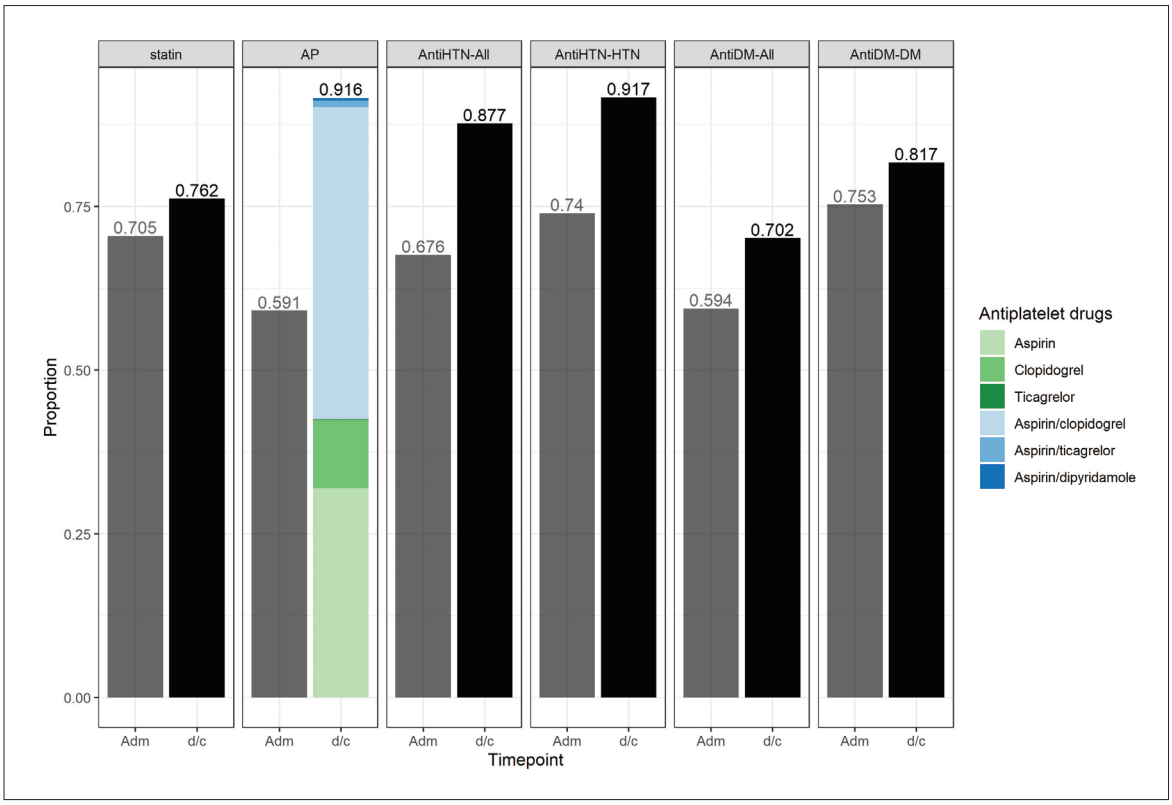

Fig. 1. Evidence-based medical therapy (EBMT) use at admission and discharge. The rates of EBMT use for each drug class at admission and discharge are shown in grey and black bars, respectively. For antiplatelets, the specific drugs are also shown. For anti-hypertensives, results are presented in both the entire cohort (AntiHTN-All) and in patients with hypertension (AntiHTN-HTN). For anti-diabetics, results are presented in both the entire cohort (AntiDM-All) and in patients with diabetes (AntiDM-DM).
Adm: admission; AntiDM: anti-diabetic; AntiHTN: anti-hypertensive; AP: antiplatelet; d/c: discharge; DM: diabetes; HTN: hypertension

P=0.043). Those who received anti-hypertensives at discharge had lower AFS (74.4% vs 85.4%, *P*=0.030) and overall survival (81.8% vs 92.1%, *P*=0.007).

To the best of our knowledge, this is the first detailed drug utilisation study of EBMT in PAD patients in Singapore, adding to the limited body of Asian data in this area.[4,5] Although prescription rates increased at discharge for all 4 drugs classes compared to rates at admission, not all patients received the recommended statin and antiplatelet. Those who were given EBMT at discharge were more likely to be taking them post-discharge. Therefore, the admission for angioplasty is a good opportunity to institute drug utilisation in patients who have not been started on the drugs or were not previously compliant.

SGH joined the Society for Vascular Surgery Vascular Quality Initiative (VQI), an international prospective registry of common vascular procedures since June 2019.[10] Initial results from 265 patients in the first 6 months of VQI data collection indicated higher pre-procedure use of statins and antiplatelets (88.3% and 81.5%, respectively) than our study.[10] Participation in VQI itself might have been an impetus for doctors to prescribe EBMT more religiously. Our results therefore reflect largely the practice before participation in VQI.

A surprising finding in our study was that limb-related outcomes and survival were worse for patients on EBMT at discharge, compared to those who were not; this association could be confounded by certain comorbidities that increased the risk of amputation and death, or procedural complexity.

There are some limitations to this study. Firstly, drugs collected from sources outside the SingHealth cluster would not be captured. However, most patients are likely to follow up within SingHealth since the angioplasty was done in SGH. Secondly, we do not know the reasons patients were not taking the EBMT drugs. Lastly, the adherence measures we report rely on dispensing records. Actual medication adherence could be lower.

In conclusion, we found suboptimal EBMT use in PAD patients undergoing angioplasty in Singapore. We are currently undertaking a qualitative study to

understand the factors behind EBMT adherence in our population to inform future interventions to improve adherence rates.

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Sze Ling Chan [1,2]*PhD*, Charyl Jia Qi Yap [3]*BSc*, Nicholas Graves [2]*PhD*, Tze Tec Chong [3]*FACS*, Tjun Yip Tang [4]*FRCS*

[1] Health Services Research Centre, SingHealth, Singapore
[2] Health Services and Systems Research, Duke-NUS Medical School, Singapore
[3] Department of Vascular Surgery, Singapore General Hospital, Singapore
[4] The Vascular and Endovascular Clinic Pte Ltd, Gleneagles Hospital, Singapore

Correspondence: Dr Sze Ling Chan, Health Services Research Centre, SingHealth, 20 College Road, Singapore 169856.
Email: chan.sze.ling@singhealth.com.sg