Maneuvering Between Scylla and Charybdis, management of antithrombotic therapy in thrombocytopenic patients with ischemic stroke

Dott. Matteo Grazzini
Clinica Neurologica Ospedale Policlinico San Martino, Genova
Thrombocytopenia is defined as a platelet count of less than $150 \times 10^3/\mu L$ (approximately 2.5 percent of the population).

People with incidentally discovered borderline thrombocytopenia may have a low incidence of progression to clinical disease.

Only 6.9% patients with platelet values between $100 \times 10^3/\mu L$ and $150 \times 10^3/\mu L$ develops more severe thrombocytopenia.

The most recognised platelet count referred for thrombocytopenia definition is $<100 \times 10^3/\mu L$ on current literature.

The incidence of thrombocytopenia in acute ischemic stroke (AIS) have been found in 7.9% of cases considering a platelet threshold $<150 \times 10^9/L$.

It was lower if considering platelet count $<100 \times 10^9/L$, ranging about 4%.

It was not suspected based on initial history in only 0.3% of patients.

Degrees of thrombocytopenia can be further subdivided into mild (platelet count 100 to $150 \times 10^3/\mu L$), moderate (50 to $99 \times 10^3/\mu L$), and severe ($<50,000 \times 10^3/\mu L$).

*However, it must be interpreted in the context of the underlying disease, and higher or lower values may be appropriate for certain conditions.
According to current US and European guidelines, PC < 100×10^9/L is a contraindication for IVT.

While US guidelines recommend initiating IVT treatment before PC is available, European guidelines do not, according to the criteria of the previous randomized IVT trials.
A platelet count <100,000/mm³ is a contraindication for the administration of intravenous alteplase for acute ischemic stroke.

This threshold was derived from expert consensus. The risk of hemorrhagic complications is expected to be increased in the setting of severe thrombocytopenia, but the precise relationship between platelet count and bleeding risk is not well studied.

Whether a platelet count of 100,000 mm³ is a justified threshold for withholding intravenous thrombolysis remains unclear. Of 14,306 stroke patients treated with intravenous alteplase, 21 patients have been reported with details; sICH was documented in 1 of these 21 patients (4.8%). The extremely small number of published cases precludes solid conclusions.

<table>
<thead>
<tr>
<th>Table 13. Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Frank et al</td>
</tr>
<tr>
<td>Meretoja et al</td>
</tr>
<tr>
<td>Brunner et al</td>
</tr>
<tr>
<td>Kvistad et al</td>
</tr>
<tr>
<td>Gensicke et al</td>
</tr>
</tbody>
</table>
Abnormal blood platelet count (BPC) on admission is correlated with greater 30-day and 90-day mortality after an acute ischemic stroke.

Sico et al. reported that thrombocytopenia on admission is independently associated with in-hospital mortality following acute ischemic stroke, even after adjusting for NIHSS and comorbidities.

Admission thrombocytopenia among patients presenting with acute ischemic stroke predicts in-hospital mortality.

Tohgi et al found that decreasing platelet counts are negatively correlated with infarct size.

There is a paucity of studies focused on the potential association between BPC and outcomes or mortality after AIS.
Several disorders can lead to thrombocytopenia. Only some of these conditions cause prothrombotic state directly. These disorders may also be overlapping. Several hematologic disorders leads to the risk of thrombotic events. Stroke has been identified in 1.27% of patients with hematologic disorders as presenting manifestation.
Several disorders can lead to thrombocytopenia with different mechanisms, resulting in a prothrombotic state and an increased risk of thrombosis. Treatment is based on the etiology and, in some cases, treating the secondary cause results in normalization of platelet counts, reducing the thrombotic risk at the same time.
Aims
We intended to assess the incidence of association between AIS and thrombocytopenia in our patient cohort and on scientific available literature, in order to evaluate the management of antithrombotic therapy, their clinical outcome and its relationship with thrombocytopenia.

Material and methods
We performed a non-systematic literature review of the pubmed database researching for all current published article providing cases of AIS experiencing thrombocytopenia (<100x10^9/L) at the time of stroke onset. Overall 54 articles have been included.

We furthermore performed retrospective analysis of available clinical records in our neurologic clinic by January 2002 until December 2018. We assessed the incidence of this association in AIS patients on admission, in order to evaluate the management of antithrombotic therapy, their clinical outcome and its relationship with thrombocytopenia.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL CASES (n=58)</strong></td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>51,8±19,6</td>
</tr>
<tr>
<td>platelet count at stroke onset, x10³/uL (mean±SD)</td>
<td>69,2±39,8</td>
</tr>
</tbody>
</table>
| Cerebrovascular risk factors                                            | Hypertension=8 (14%)  
Dyslipidemia n=4 (7%)  
AF n=6 (10%)  
DM n=3 (5%)  
Previous Stroke/TIA n=9 (15,5%)  
ACS n=2 (3%)  
Atherosclerosis n=2 (3%)  
Smoking n=3 (5%)  
Others n=8 (14%)  
None n= 18 (31%)                                                                 |
| Treatment for thrombocytopenia                                          | Steroid n=23 (40%)  
PEx n=9 (15,5%)  
IVIG n=11 (19%)  
PLT transfusion n=5(9%)  
immunosuppressant n=10 (17%)  
Splenectomy n=6 (10%)  
EPO n=1 (1,7%)  
antithrombotic therapy discontinuation n=5 (9%)  
None n=9 (15,5%)  
NA n=15 (26%)                                                                 |
| Treatment of AIS                                                         | ASA n=5 (8,6%)  
Clopidogrel n=1 (1,7%)  
Cilostazol n=1 (1,7%)  
Sodium ozagrel n=2 (3%)  
ASA+dipyridamole n=1 (1,7%)  
ASA+clopidogrel n=2 (3%)  
AP not specified n=3 (5%)  
Fondaparinux n=3 (5%)  
Argatroban n=1 (1,7%)  
Tirofiban n=1 (1,7%)  
ACO n=8 (14%)  
AP+ACO n=2 (3%)  
Heparin n=6 (10%)  
CEA n=2 (3%)  
IVT n=2 (3%)  
IA Thrombolysis n=1 (1,7%)  
Mechanical thrombectomy (MT) n=1 (1,7%)  
IAT+TM n=1 (1,7%)  
None n=8 (14%)  
NA n=13 (22%)                                                                 |
| NIHSS at admission (mean)                                               | 8                                                                                           |
| NIHSS at discharge (mean)                                               | 4                                                                                           |
| TOAST classification                                                     | LAA n=10 (17%)  
SVO n=2 (3%)  
CE n=4 (7%)  
UD n= 20 (34%)  
OD n=6 (10%)  
NA n=16 (27,5%)                                                                 |
| ICH                                                                      | Yes n=5 (9%)  
No n=28 (48%)  
NA n=25 (43%)                                                                 |
| Follow up (3 months mRS)                                                | mRS0 n=7 (12%)  
mRS1 n=6 (10%)  
mRS2 n=2 (3%)  
mRS3 n=1 (2%)  
mRS4 n=2 (3%)  
mRS5 n=2 (3%)  
mRS6 n=4 (7%)  
NA n=34 (59%)                                                                 |
Causes of thrombocytopenia

Study population (n=58)

- ITP
- TTP
- APS
- HIT
- DIC
- Cancer
- Unspecified
- Miscellany

ICH (9%)
- n=1
- n=1
- n=1

Platelet count x10^3/uL
- 90
- 113
- 23.6
- 48
- <100
In a relevant percentage of patients having less than $50 \times 10^9 / L$ platelet none antithrombotic therapy was administered.
ITP patients experienced AIS soon after IGV therapy in several cases. Many TTP patient were treated only with PEX and no antithrombotic therapy.
Clinical outcome
### Reports on IVT-treated stroke patients with PC <100 × 10^9/L in current literature

<table>
<thead>
<tr>
<th>Author</th>
<th>year of publication</th>
<th>number of cases/sex</th>
<th>Age</th>
<th>PLT x10³/uL (Lowest)</th>
<th>NIHSS admission/discharge</th>
<th>STN</th>
<th>Large vessels occlusion</th>
<th>ICH</th>
<th>SICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mowla A. et al</td>
<td>2017</td>
<td>5/2F</td>
<td>75 ± 18</td>
<td>63 ± 19</td>
<td>10 (range 5-17)</td>
<td>165' (n=1)</td>
<td>NA</td>
<td>n=1</td>
<td>n=1</td>
</tr>
<tr>
<td>Meretoja A. et al</td>
<td>2010</td>
<td>7/NA</td>
<td>72,7</td>
<td>&lt;100</td>
<td>13 ± 4,7</td>
<td>153' ± 61'</td>
<td>NA</td>
<td>n=1</td>
<td>n=1</td>
</tr>
<tr>
<td>Brunner F. et al</td>
<td>2011</td>
<td>3/NA</td>
<td>NA</td>
<td>82 (59)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Kvistad CE. Et al</td>
<td>2013</td>
<td>1/NA</td>
<td>77,4 ± 11,9</td>
<td>&lt;100</td>
<td>9 (range 5-16)</td>
<td>NA</td>
<td>NA</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Frank B. et al</td>
<td>2013</td>
<td>10/NA</td>
<td>NA</td>
<td>&lt;100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>De Piazza C. et al</td>
<td>2016</td>
<td>1/F</td>
<td>63</td>
<td>71</td>
<td>9/14</td>
<td>210'</td>
<td>left MCA</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Camara-Lemarroy C.R. et al</td>
<td>2016</td>
<td>1/F</td>
<td>22</td>
<td>23,6</td>
<td>10/0</td>
<td>150'</td>
<td>[rtPA using 0.6mg/kg]</td>
<td>right MCA</td>
<td>yes</td>
</tr>
<tr>
<td>Boattini M.</td>
<td>2013</td>
<td>1/M</td>
<td>39</td>
<td>27</td>
<td>4/0</td>
<td>100'</td>
<td>left MCA-M2</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Breuer L et al</td>
<td>2013</td>
<td>3/1F</td>
<td>case 1 (65), case 2 (64), case 3 (78)</td>
<td>case 1: 59, case 2: 90, case 3: 96</td>
<td>case 1 (14), case 2 (5), case 3 (7)</td>
<td>NA</td>
<td>NA</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Gensicke H et al</td>
<td>2018</td>
<td>44/12F</td>
<td>66 (59-79)</td>
<td>83 (29), &lt;50 n=2 not reporting ICH</td>
<td>13 (7-18 range)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>n=3</td>
</tr>
</tbody>
</table>

**Tot n=76   SICH n=5**  (PLT n1: 48x10³/uL, n2 NA, n3 & n4 ≥50x10³/uL)
Our study population

<table>
<thead>
<tr>
<th>TOTAL CASES (n=28)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>51 ±20</td>
</tr>
<tr>
<td>platelet count at stroke onset, x10³/uL (mean±SD)</td>
<td>69±40</td>
</tr>
<tr>
<td>CHA2DS2-VASc Score (mean±SD)</td>
<td>4±2</td>
</tr>
<tr>
<td>Large Vessel intracranial Occlusion</td>
<td>n=8</td>
</tr>
<tr>
<td>NIHSS admission (mean±SD)</td>
<td>8±7</td>
</tr>
<tr>
<td>ICH</td>
<td>n=5</td>
</tr>
<tr>
<td>SICH</td>
<td>0</td>
</tr>
<tr>
<td>inhospital mortality</td>
<td>7 (25%)</td>
</tr>
</tbody>
</table>

PLT level (x10³/uL): 100 (n=2); 80 (n=1); 74 (n=1); 73 (n=1)
IVT-treated stroke patients with PC <100 × 10⁹/L

<table>
<thead>
<tr>
<th></th>
<th>Platelet count x10³/uL</th>
<th>revascularization</th>
<th>NIHSS before/after treatment</th>
<th>ICH</th>
<th>mRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>95</td>
<td>IVT+MT</td>
<td>21/3</td>
<td>no</td>
<td>2</td>
</tr>
<tr>
<td>Case 2</td>
<td>80</td>
<td>IVT+MT</td>
<td>8/4</td>
<td>HI2</td>
<td>2</td>
</tr>
<tr>
<td>Case 3</td>
<td>87</td>
<td>IV</td>
<td>5/2</td>
<td>no</td>
<td>0</td>
</tr>
<tr>
<td>Case 4</td>
<td>100</td>
<td>IV</td>
<td>23/19</td>
<td>HI1</td>
<td>5</td>
</tr>
<tr>
<td>Case 5</td>
<td>38</td>
<td>MT</td>
<td>20/20</td>
<td>no</td>
<td>6</td>
</tr>
</tbody>
</table>
Take home message I

In case of asymptomatic moderate thrombocytopenia, follow up and platelet count repetition in one to two weeks can be considered.

In young patients experiencing CVE, hematological autoimmune disorders should be considered. Platelets aggregation and thrombosis are not wide spreading in early stages, therefore thrombocytopenia and other signs may not be clinically evident at first.

A systematic review estimated the frequency of aPL in young patients with cerebrovascular events (CVE) of undetermined origin at 17%, rising up to 22% for aCL in patients with stroke; its persistence with high title over time confers an higher thrombotic risk.

Patient older than 60 yrs with persistent thrombocytopenia should be evaluated for occult cancer.

Platelets destruction leads to quick turn-over and younger platelet are thrombotically more active, a quick raising on platelet counts may increases the risk of thrombotic complications. Therapies used to treat immune thrombocytopenia like intravenous immunoglobulin (IVIg) may also play a role.

It should be remembered that in case of HIT-II the risk of thrombosis remains high for 4–6 weeks after. Warfarin is not recommended because of the risk of paradox worsening and alternative anticoagulant should be given for up to 4 weeks, Fondaparinux is the more commonly available.
Reducing anticoagulation dose is possibly safe (bleeding), but efficacy (i.e. rates of thrombosis) is not known. Patients with platelet counts greater than 50 ×10^3/μL rarely have symptoms.

When platelets are above 50×10^9/L, full dose anticoagulation (OAC) appears safe, representing a trigger for changes in management of OAC. Current guidelines on VTE as well as the International Society on Thrombosis and Haemostasis (ISTH) guidelines recommend a minimum platelet count of <50×10^9/L for administer DOACs in patients with chemotherapy-induced thrombocytopenia.

In general, LMWH and direct oral anticoagulants (DOACs) are both acceptable treatment options for patients with cancer-associated thrombosis. Guidelines prioritize LMWH over DOACs in patients at high risk of bleeding. An algorithm derived from cancer patients, has been also proposed even for ITP patients (Matzdorff et al).

Management of OAC in those patients also affected with AF has only been described in anecdotal case reports. Decision making should take into account the individual thrombotic and bleeding risk. The risk benefit-ratio may change if the thrombocytopenia lasts more than several days to weeks.

However, patients with thrombocytopenia have been generally excluded from clinical trials and the generalizability of these data is limited. Clinical trials are needed to address pressing clinical questions related to the use of OAC in patients with thrombocytopenia.
Antiplatelet therapy increases bleeding risk, especially dual antiplatelet therapy (2.0% vs. 1.3% with antiplatelet monotherapy; P, 0.001), with bleeding rates that are similar to those on OAC.

In contrast, with ASA seems to be no difference in bleeding risk above and below 50×10^9/L, meaning that the risk for bleeding with ASA may increase at a lower platelet threshold.

The study by Feher et al, does however suggest that stopping all APT at count of 50×10^9/L may not be appropriate for all patients in this setting, and that a lower threshold could be considered.

The Society for Cardiovascular Angiography and Interventions proposed ASA administration with platelet counts above 10×10^9/L in patients with ACS and PCI, and reserved DAPT for counts above 30×10^9/L.

For patients with platelets counts of 50–100×10^9/L who undergo PCI, the authors recommended the following: restrict DAPT to one month post stenting. Protein pump inhibitors should be used in all patients continuing APT.

The choice of platelet transfusions in order to continuing APT or AC is not supported by any no evidence. The multiple risks of platelet transfusion should to be keep in mind in order to prevent new ischaemic events.

Platelet transfusions have to be used prophylactically at a platelet threshold of < 10 × 10^9/L to reduce bleeding risk. Higher thresholds may be considered in specific circumstances.

The relationship between platelet count and bleeding is complex and non linear. Treatment of the underlying condition may lead to rising platelet count, reducing thrombotic risk and preventing the need for antithrombotic therapy withdrawal.
Conclusions

• Platelet count ranging between 50x10^9/L may be an adequate threshold for changes in anticoagulation and it may be lower for antiplatelet therapy.

• Platelet counts remain poor predictors of bleeding for mild to moderate reduced level and the risk-benefit ratio may change in different setting.

• The proper therapeutic management should be tailored on each individual patient, taking into account their ischemic and bleeding risk as well as the underlying disease leading to thrombocytopenia.

• The relationship between platelet count and bleeding seems to be nonlinear, appearing a poor predictor of bleeding. Perhaps IVT may be safe at moderate low platelet count at least in some patients.

• Little data are available yet and it precludes solid conclusions. Further evidence is needed to support this practice. Clinical guidelines are also needed to standardize and streamline clinical practice in these challenging settings.