Triple antithrombotic therapy：DAPT＋抗凝固療法のリスク（161012）

AF の患者が PCI を受けることだって多い。でも、DAPT＋抗凝固薬という組み合わせは、出血という点から考えるとかなりハイリスクのようにも見える。もちろん、こういう治療は効果と副作用のバランスを正味の利益で考えなければならない。

3 剤併用のリスクについての論文をいくつか読んでみた。

まず一つ目。PCI を行った患者のコホート。ほとんどの患者が退院時には DAPT が行われているような集団だ。

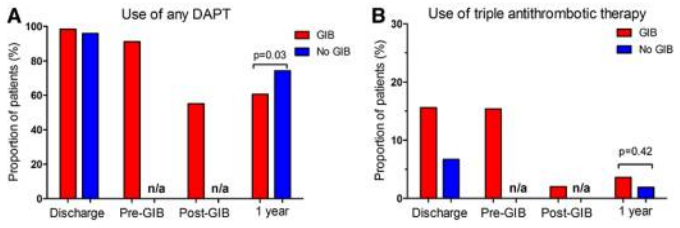

Figure 3. Use of dual antiplatelet therapy (DAPT; **A**), triple antithrombotic therapy (**B**), and proton pump inhibitors (**C**) at discharge, immediately preceding and after the gastrointestinal bleeding (GIB) event, and at 1 year. For patients without GIB, rates of medication use are shown at discharge and at 1 year. Difference between groups are compared at 1-year follow-up. n/a indicates not applicable.

結果は triple antithrombotic therapy が独立した消化管出血のリスクとされる。HR は 2.48 なので、出血リスクの高い集団にとってはそれなりに大きなインパクトがあると思う。ちなみに、喫煙は 2.49、消化管出血の既往は 3.28、癌の既往は 2.17 と報告されている。

METHODS AND RESULTS:
Between 2009 and 2012, all consecutive patients undergoing PCI were prospectively included in the Bern PCI Registry. Bleeding Academic Research Consortium (BARC) GIB and cardiovascular outcomes were recorded within 1 year of follow-up. Among 6212 patients, 84.1% received new-generation drug-eluting stents and 19.5% received prasugrel. At 1 year, GIB had occurred in 65 patients (1.04%); 70.8% of all events and 84.4% of BARC ≥ 3B events were recorded > 30 days after PCI. The majority of events (64.4%) were related to upper GIB with a more delayed time course compared with lower GIB. Increasing age, previous GIB, history of malignancy, smoking, and triple antithrombotic therapy (ie, oral anticoagulation plus dual antiplatelet therapy) were independent predictors of GIB in multivariable analysis. GIB was associated with increased all-cause mortality (adjusted hazard ratio, 3.40; 95% confidence interval, 1.67-6.92; P = 0.001) and the composite of death, myocardial infarction, or stroke (adjusted hazard ratio, 3.75; 95% confidence interval, 1.99-7.07; P < 0.001) and was an independent predictor of all-cause mortality during 1 year.

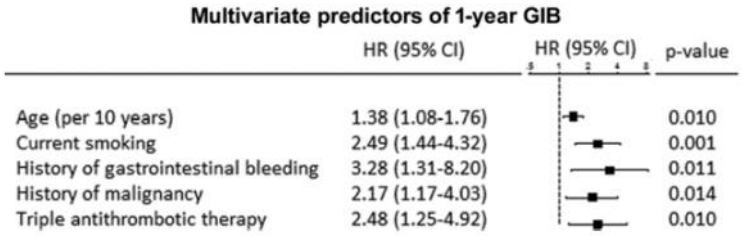

Figure 4. Multivariable predictors of 1-year gastrointestinal bleeding (GIB). CI indicates confidence interval; and HR, hazard ratio.

（参考文献 1 より引用）

文献 2 はクロピドグレルの投与期間を検討した RCT。3 剤併用の副作用についても参考になりそうなので読んでみる。

●PECO

P：patients receiving OAC who underwent DES implantation at 3 European centers between September 2008 and December 2013.（patients receiving concomitant aspirin and OAC）
E：6-week clopidogrel therapy (n=307)
C：6-month clopidogrel therapy (n=307)
O：The primary endpoint was a composite of death, myocardial infarction (MI), definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months.

oral anticoagulation (OAC) , drug-eluting stent (DES)

抗凝固薬服用中で DES 留置を行った患者に対して、aspirin に加えて 6 週間の clopidogrel を投与した場合、6 か月の clopidogrel を投与した場合と比較して、9 か月時点での正味の臨床的利益（死亡、心筋梗塞、ステント血栓症、TIMI 大出血）が改善するかどうかを検討した試験である。

●妥当か

抄録中に randomized, open-label trial とあり、本文には Patients were considered enrolled in the study and eligible for the final intention-to-treat analysis at the time of randomization.の記載がある。

●結果

6 週間群と 6 か月群に差はなかった。

出血に関しても差はなかった。

The primary endpoint occurred in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (hazard ratio [HR]: 1.14; 95% CI: 0.68 to 1.91; p=0.63). There were no significant differences for the secondary combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, and ischemic stroke (12 [4.0%] vs. 13 [4.3%]; HR: 0.93; 95% CI: 0.43 to 2.05; p=0.87) or the secondary bleeding endpoint of TIMI major bleeding (16 [5.3%] vs. 12 [4.0%]; HR: 1.35; 95% CI: 0.64 to 2.84; p=0.44).

Six weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes. These results suggest that physicians should weigh the trade-off between ischemic and bleeding risk when choosing the shorter or longer duration of triple therapy.

TABLE 3 Results for Primary and Secondary Endpoints at 9 Months and in Landmark Analysis From 6 Weeks to 9 Months

	Outcome at 9 Months				Landmark	
	6-Week Group (n = 307)	6-Month Group (n = 307)	Hazard Ratio (95% CI)	p Value	6-Week Group	6-M Gr
Primary endpoint						
Death, MI, stent thrombosis, stroke or major bleeding	30 (9.8)	27 (8.8)	1.14 (0.68-1.91)	0.63	13 (4.6)	19 (
Secondary endpoints						
Cardiac death, myocardial infarction stent thrombosis or ischemic stroke	12 (4.0)	13 (4.3)	0.93 (0.43-2.05)	0.87	4 (1.4)	10 (
TIMI major bleeding	16 (5.3)	12 (4.0)	1.35 (0.64-2.84)	0.44	7 (2.4)	7 (
Death	12 (4.0)	16 (5.2)	0.75 (0.35-1.59)	0.45	8 (2.7)	12 (
Cardiac death	5 (1.7)	9 (3.0)	0.56 (0.19-1.66)	0.29	3 (1.0)	8 (
MI	6 (2.0)	0	–	0.03	1 (0.03)	
Periprocedural MI	3 (1.0)	0	–	0.25	–	
Definite stent thrombosis	2 (0.7)	0	–	0.50	0	
Stroke	4 (1.3)	6 (2.0)	0.67 (0.19-2.35)	0.53	2 (0.7)	2 (
Ischemic stroke	3 (1.0)	4 (1.3)	0.75 (0.17-3.34)	0.71	1 (0.03)	2 (
TIMI major and minor bleeding	35 (11.5)	30 (9.9)	1.18 (0.73-1.93)	0.49	14 (5.0)	15 (
TIMI major bleeding	16 (5.3)	12 (4.0)	1.35 (0.64-2.84)	0.44	7 (2.4)	7 (
TIMI minor bleeding	19 (6.3)	18 (5.9)	1.06 (0.56-2.03)	0.85	7 (2.4)	8 (
Any BARC bleeding	114 (37.6)	122 (40.2)	0.94 (0.73-1.21)	0.63	48 (20.5)	70 (
BARC 1	58 (19.4)	57 (19.1)	1.03 (0.72-1.49)	0.87	28 (10.6)	37 (
BARC 2	22 (7.3)	33 (10.9)	0.66 (0.38-1.13)	0.13	7 (2.5)	17 (
BARC 3a	14 (4.6)	17 (5.6)	0.83 (0.41-1.68)	0.60	4 (1.4)	8 (
BARC 3b	17 (5.6)	13 (4.3)	1.32 (0.64-2.72)	0.45	7 (2.4)	8 (
BARC 3c	0	0	–	–	0	
BARC 4	0	0	–	–	0	
BARC 5a	0	1 (0.03)	–	>0.99	0	
BARC 5b	3 (1.0)	1 (0.03)	3.00 (0.34-25.8)	0.34	2 (0.7)	
BARC bleeding ≥ 2	56 (18.4)	65 (21.3)	0.86 (0.60-1.23)	0.41	20 (7.6)	33 (

Values are n (Kaplan Meier Estimates), unless otherwise noted.
BARC = Bleeding Academic Research Consortium criteria; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction criteria.

（参考文献 2 より引用）

ただし、ここでは、複合イベントの結果の比較というより、各群でどれくらいの出血イベントがあったのかを確認しておくのが目的に叶う。

TIMI 出血基準の小出血＋大出血は 9.9～11.5%、BARC 出血基準で 2 以上の出血は 18.4～21.3%程度である。何らかの医学的な対応が望ましい出血が 2 割もあるとすれば、かなりハイリスクと考えていいと思う。

もう一本、Lancet の RCT である WOEST 試験から。

●PECO

P：adults receiving oral anticoagulants and undergoing PCI
E：clopidogrel alone (double therapy)
C：clopidogrel plus aspirin (triple therapy).
O：The primary outcome was any bleeding episode within 1 year of PCI

経口抗凝固薬服用中で、PCI を施行した成人患者に対して、clopidogrel を単独で投与すると、clopidogrel と aspirin を併用して投与する場合と比較して、PCI 後 1 年以内の出血エピソードが減少するかどうかを検討した試験であることがわかる。

●妥当か

抄録中に、Randomised、assessed by intention to treat などの記載がある。

●結果

出血イベントは double therapy 群で 19.4%であったのに対し、triple therapy 群では 44.4%であり、double therapy 群で 64%低い。

Bleeding episodes were seen in 54 (19·4%) patients receiving double therapy and in 126 (44·4%) receiving triple therapy (hazard ratio [HR] 0·36, 95% CI 0·26–0·50, p<0·0001). In the double–therapy group, six (2·2%) patients had multiple bleeding events, compared with 34 (12·0%) in the triple–therapy group. 11 (3·9%) patients receiving double therapy required at least one blood transfusion,

compared with 27 (9·5%) patients in the triple-therapy group (odds ratio from Kaplan-Meier curve 0·39, 95% CI 0·17-0·84, p=0·011).

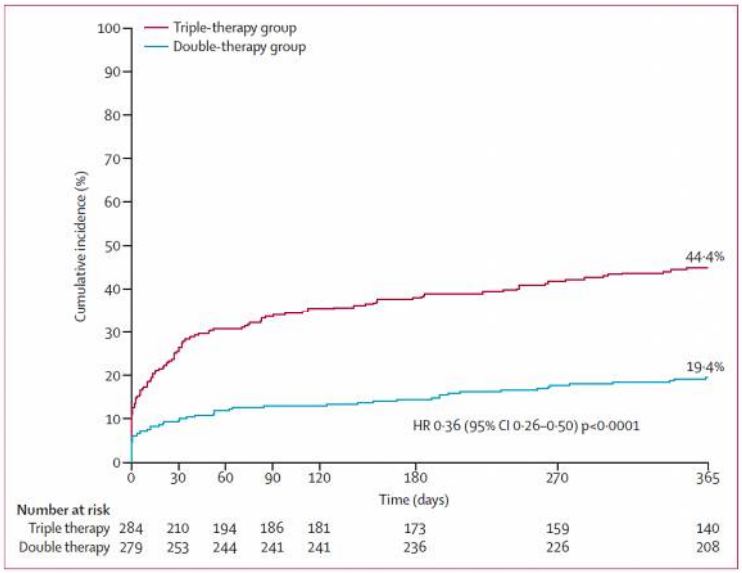

Figure 2: Incidence of the primary endpoint (any bleeding)
HR=hazard ratio.

（参考文献 3 より引用）

ま、double therapy 群より、triple therapy 群で出血が多いことは予想できる。TIMI 出血基準の大出血+小出血は triple therapy 群で 31.3%であり、BARC 出血基準で 2+3 は 31.7%と記載されている。

3 剤併用療法は出血が増加するが、1 年で 30%なんていう驚きの報告もあるので、ハイリスクであることは間違いない。ただ、思いのほかリスクは高いように思う。患者によって程度の差はあると思うが、基本的に予防をしっかりする必要があると思う。

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