ORIGINAL ARTICLE

# Safety profile of prasugrel and clopidogrel in patients with acute coronary syndromes in Switzerland

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2014-306925).

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Received 9 October 2014
Revised 15 January 2015
Accepted 28 February 2015
Published Online First
20 March 2015

## ABSTRACT

**Objective** To assess safety up to 1 year of follow-up associated with prasugrel and clopidogrel use in a prospective cohort of patients with acute coronary syndromes (ACS).

**Methods** Between 2009 and 2012, 2286 patients invasively managed for ACS were enrolled in the multicentre Swiss ACS Bleeding Cohort, among whom 2148 patients received either prasugrel or clopidogrel according to current guidelines. Patients with ST-elevation myocardial infarction (STEMI) preferentially received prasugrel, while those with non-STEMI, a history of stroke or transient ischaemic attack, age ≥75 years, or weight <60 kg received clopidogrel or reduced dose of prasugrel to comply with the prasugrel label.

**Results** After adjustment using propensity scores, the primary end point of clinically relevant bleeding events (defined as the composite of Bleeding Academic Research Consortium, BARC, type 3, 4 or 5 bleeding) at 1 year, occurred at a similar rate in both patient groups (prasugrel/clopidogrel: 3.8%/5.5%). Stratified analyses in subgroups including patients with STEMI yielded a similar safety profile. After adjusting for baseline variables, no relevant differences in major adverse cardiovascular and cerebrovascular events were observed at 1 year (prasugrel/clopidogrel: cardiac death 2.6%/4.2%, myocardial infarction 2.7%/3.8%, revascularisation 5.9%/6.7%, stroke 1.0%/1.6%). Of note, this study was not designed to compare efficacy between prasugrel and clopidogrel.

**Conclusions** In this large prospective ACS cohort, patients treated with prasugrel according to current guidelines (ie, in patients without cerebrovascular disease, old age or underweight) had a similar safety profile compared with patients treated with clopidogrel.

**Clinical trial registration number** SPUM-ACS: NCT01000701; COMFORTABLE AMI: NCT00962416.

Linked

▶ http://dx.doi.org/10.1136/heartjnl-2014-307356

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**To cite:** Klingenberg R, Heg D, Räber L, *et al*. *Heart* 2015;**101**:854–863.

## INTRODUCTION

Prasugrel, a thienopyridine, is a prodrug that, like clopidogrel, requires conversion into an active metabolite before binding to the $P_2Y_{12}$ platelet receptor to confer antiplatelet activity. Yet, prasugrel inhibits platelet ADP-induced platelet aggregation more rapidly and more consistently than clopidogrel.[1 2] The TRial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet InhibitioN with Prasugrel—Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) showed a benefit in the primary efficacy end point (death from cardiovascular causes, myocardial infarction or stroke) at the expense of an increase in serious bleeding (primary safety end point) of prasugrel versus clopidogrel in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI).[3] Of note, patients with diabetes and patients with ST-elevation myocardial infarction (STEMI) had a marked benefit in terms of ischaemic event reduction without an increase in rates of major bleeding.[4 5] Based on these data, the US Food and Drug Administration and the European Medicines Agency approved prasugrel for patients with ACS. Prasugrel is contraindicated in patients with prior stroke or transient ischaemic attack (TIA) because there was a net clinical benefit in favour of clopidogrel. In Europe, based on pharmacodynamic data, a lower maintenance dose of 5 mg is recommended in patients ≥75 years old and/or <60 kg body weight,[6 7] as those patients showed an increased risk of bleeding and no difference for ischaemic events.[8] Thus, the most recent ACS guidelines of the European Society of Cardiology assigned a class IB recommendation to the use of prasugrel in $P_2Y_{12}$-inhibitor-naïve patients (diabetics in particular) with known coronary anatomy scheduled for PCI unless there is a high risk of life-threatening bleeding or other contraindications.[6]

At present, beyond prescription patterns,[9 10] outcome data on prasugrel compared with clopidogrel in patients with ACS referred for coronary angiography outside of a randomised trial design are scarce.[11–13] Currently, no data were reported in an ACS-PCI cohort with independently adjudicated long-term outcome. Furthermore, data on bleeding events assessed simultaneously according to three major classifications, the TIMI score,[14] the Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)[15] score as well as the recent Bleeding Academic Research Consortium (BARC)[16] score in patients with ACS treated with prasugrel or clopidogrel are currently not available.

The aim of this study was to assess safety and effectiveness of prasugrel and clopidogrel in a 'real-world' prospective cohort of patients with ACS outside of a randomised controlled trial using three common classifications to assess bleeding events occurring until 12 months after initial presentation.

## METHODS

### Patient characteristics

Patients recruited at four Swiss centres as part of the Swiss ACS Bleeding Cohort (including those enrolled in parallel in the COMFORTABLE AMI trial)[17] between September 2009 and October 2012 with an adjudicated follow-up for events occurring ≤1 year (≤365 days) were considered for this study. The Swiss ACS Bleeding Cohort is part of the Special Program University Medicine and recruited patients who were referred for coronary angiography with the diagnosis of ACS to one of the participating University Hospitals (Zurich, Bern, Lausanne, Geneva). This prospective multicentre cohort comprised consecutive recruitment and follow-up performed at 30 days (phone call) and 1 year (clinical visit). Women and men aged 18 years and older presenting within 5 days (preferably within 72 h) after pain onset with the main diagnosis of STEMI, non-STEMI or unstable angina, irrespective of prior use of prasugrel or clopidogrel were included in this study. Included patients had symptoms compatible with angina pectoris (chest pain, dyspnoea) and fulfilled at least one of the following criteria: (A) persistent ST segment elevation or depression, T-inversion or dynamic ECG changes, new left bundle branch block; (B) evidence of positive troponin by local laboratory reference values with a rise and/or fall in serial troponin levels; (C) known coronary artery disease, specified as status after myocardial infarction, coronary artery bypass graft (CABG) or PCI, or newly documented ≥50% stenosis of an epicardial coronary artery during the initial catheterisation. Exclusion criteria comprised severe physical disability, inability to comprehend study or less than 1 year of life expectancy for non-cardiac reasons.

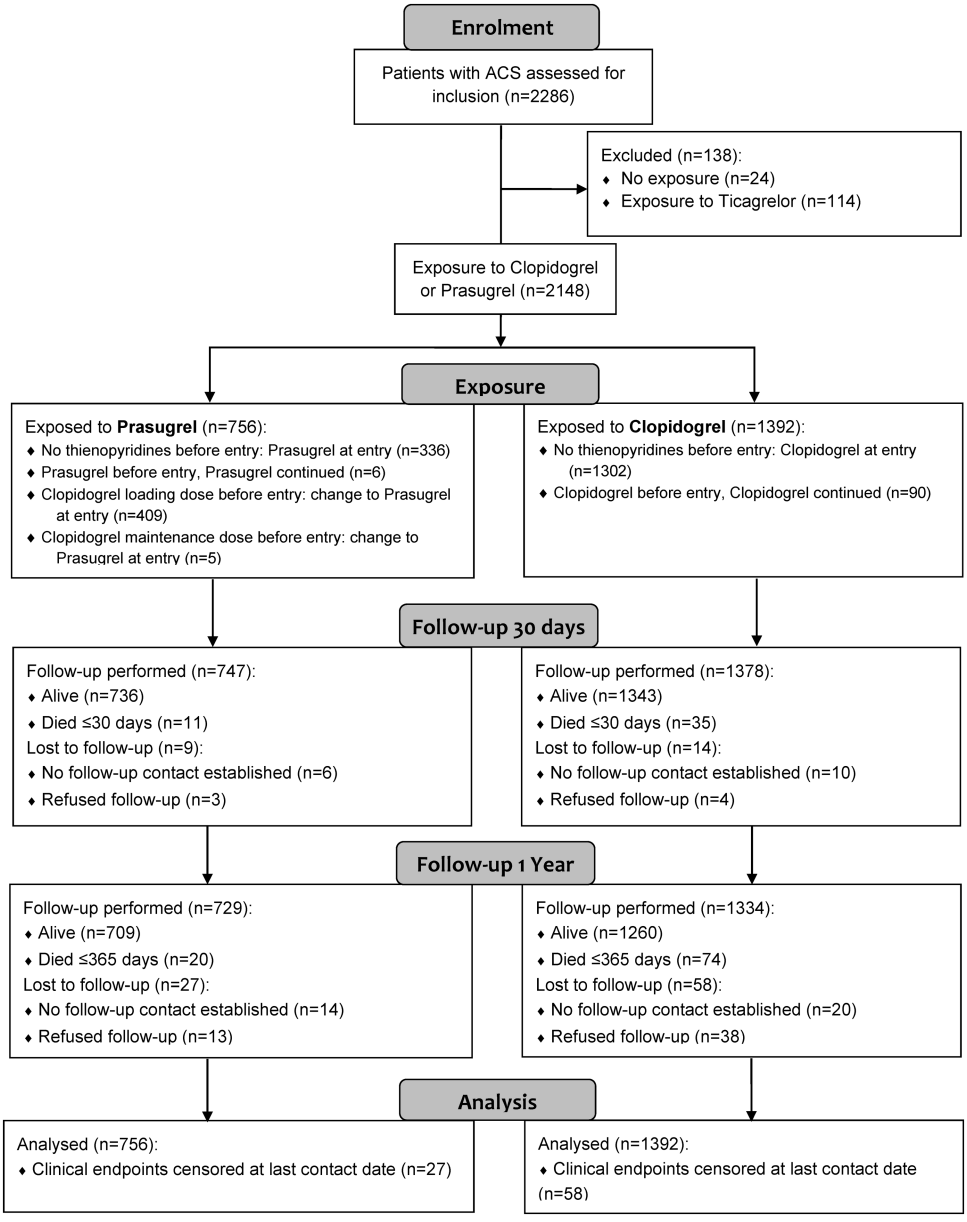


**Figure 1** Study design. The flow chart shows the distribution of patients on prasugrel (n=756), clopidogrel (n=1392) and ticagrelor (n=114) in the prospective cohort during 1 year follow-up. ACS, acute coronary syndrome.

Nested into the Swiss ACS Bleeding Cohort at the Swiss centres, the COMFORTABLE AMI trial compared the effects of a biolimus-eluting stent carrying a biodegradable polymer with a bare metal stent on cardiovascular outcomes in patients with STEMI defined by chest pain onset ≤24 h and persistent ST segment elevation or new left bundle branch block.[17] Follow-up was performed at 30 days (phone call) and 12 months (clinical visit), respectively.

### Medications

The protocol for medications during hospital stay and follow-up comprised administration of aspirin and an additional platelet inhibitor (prasugrel, clopidogrel or ticagrelor) for 1 year after the ACS unless an indication for oral anticoagulation was present. Patients received prasugrel, ticagrelor or clopidogrel at the discretion of the treating cardiologist with a preference for prasugrel by consensus in patients with STEMI.[5] Dosing and duration of administration of either drug was at the discretion of the treating cardiologist, with a recommendation to follow current dosing guidelines (prasugrel 10 mg or 5 mg daily as indicated according to the label, ticagrelor 90 mg twice daily, clopidogrel 75 mg daily).[6 7] Treating physicians were advised to administer a statin, an ACE inhibitor or angiotensin II receptor-blocker and a β-blocker as soon after the ACS as tolerated by the patient.

### Bleeding events

The prespecified primary safety end point was a clinically relevant bleeding event, defined as the composite of either BARC type 3, 4 or 5 bleeding incident during 1 year follow-up.

**Table 1** Baseline characteristics

| Total number of patients | Prasugrel N=756 | Clopidogrel N=1392 | p Value |
|---|---|---|---|
| Age (years) | n=756, 58.65±10.99 | n=1392, 66.07±12.49 | <0.001 |
| ≥75 years | n=756, 57 (7.5%) | n=1392, 409 (29.4%) | <0.001 |
| Gender (female) | n=756, 117 (15.5%) | n=1392, 338 (24.3%) | <0.001 |
| Weight (kg) | n=742, 82.27±14.36 | n=1371, 79.29±15.35 | <0.001 |
| <60 kg | n=742, 22 (3.0%) | n=1371, 102 (7.4%) | <0.001 |
| Body mass index (kg/m²) | n=740, 27.45±4.24 | n=1369, 26.96±4.35 | 0.012 |
| Medical history | | | |
| Diabetes mellitus | n=756, 107 (14.2%) | n=1392, 276 (19.8%) | 0.001 |
| Hypertension | n=756, 360 (47.6%) | n=1392, 871 (62.6%) | <0.001 |
| Hypercholesterolaemia | n=754, 412 (54.6%) | n=1389, 893 (64.3%) | <0.001 |
| Current smoker | n=737, 371 (50.3%) | n=1358, 492 (36.2%) | <0.001 |
| Family history of CAD | n=745, 184 (24.7%) | n=1358, 359 (26.4%) | 0.405 |
| Glomerular filtration rate* | n=750, 98.32±25.88 | n=1377, 86.32±27.15 | <0.001 |
| Renal failure* | n=750, 50 (6.7%) | n=1377, 216 (15.7%) | <0.001 |
| History of stroke or TIA | n=756, 10 (1.3%) | n=1392, 67 (4.8%) | <0.001 |
| Previous myocardial infarction | n=754, 71 (9.4%) | n=1392, 229 (16.5%) | <0.001 |
| Previous PCI | n=756, 86 (11.4%) | n=1391, 265 (19.1%) | <0.001 |
| Previous CABG | n=756, 21 (2.8%) | n=1392, 92 (6.6%) | <0.001 |
| Clinically relevant valvular disease | n=756, 4 (0.5%) | n=1392, 27 (1.9%) | 0.008 |
| Clinical presentation | n=756 | n=1390 | <0.001 |
| Unstable angina | 9 (1.2%) | 69 (5.0%) | <0.001 |
| Non-STEMI | 85 (11.2%) | 741 (53.3%) | <0.001 |
| STEMI | 662 (87.6%) | 580 (41.7%) | <0.001 |
| Killip II, III or IV | n=752, 108 (14.4%) | n=1378, 166 (12.0%) | 0.136 |
| *Index procedure* | | | |
| PCI performed? | n=756, 747 (98.8%) | n=1392, 1278 (91.8%) | <0.001 |
| Stenting | n=747, 723 (96.8%) | n=1278, 1155 (90.4%) | <0.001 |
| Any drug-eluting stent | n=747, 561 (75.1%) | n=1278, 916 (71.7%) | 0.097 |
| Any bare metal stent | n=747, 180 (24.1%) | n=1278, 246 (19.2%) | 0.011 |
| CABG | n=747, 2 (0.3%) | n=1278, 63 (4.9%) | <0.001 |
| Antithrombins during PCI | | | |
| Unfractionated heparin | n=755, 739 (97.9%) | n=1389, 1323 (95.2%) | 0.002 |
| LMWH | n=755, 28 (3.7%) | n=1392, 88 (6.3%) | 0.012 |
| Bivalirudin | n=755, 33 (4.4%) | n=1392, 62 (4.5%) | 1.000 |
| Glycoprotein IIb/IIIa antagonists | n=755, 242 (32.1%) | n=1392, 382 (27.4%) | 0.025 |
| Baseline medication | | | |
| Proton-pump inhibitor | n=749, 78 (10.4%) | n=1385, 233 (16.8%) | <0.001 |
| Oral anticoagulation | n=749, 7 (0.9%) | n=1385, 66 (4.8%) | <0.001 |

Depicted are counts (%) or means±SDs.
*Based on creatine-estimated glomerular filtration rate clearance of <60 mL/min/1.73 m², using the Modification of Diet in Renal Disease (MDRD) formula.
CABG, coronary artery bypass graft; CAD, coronary artery disease; LMWH, low-molecular weight heparin; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischaemic attack.

Secondary end points comprised overall bleeding events graded by severity using the TIMI.[14] GUSTO[15] and BARC[16] classifications, respectively. BARC type 1 and 2 events were analysed, but not included in our analyses given inconsistent reporting. Access route was preferentially femoral in three of the four centres (Bern, Lausanne, Zurich) and radial in many patients in Geneva. Bleeding events were defined as 'inhospital' as time between enrolment and hospital discharge, '30 days' as time between enrolment and 30 days follow-up and '1 year' as time between enrolment and 1 year follow-up.

### Major adverse cardiovascular and cerebrovascular events

Individual components of major adverse cardiovascular and cerebrovascular events (MACCE) comprised death (cardiac, vascular, non-cardiovascular), myocardial infarction (European Society of Cardiology (ESC) classification),[6] repeat coronary revascularisation (any, ischaemia-driven), definite stent thrombosis,[18] cerebrovascular events comprising stroke (any, ischaemic, haemorrhagic, unclear aetiology) or TIA.

All events (bleeding and MACCE) were adjudicated by external experts who were blinded with respect to the treatment group; identical prespecified event adjudication forms were used.

### Statistical analyses

Continuous variables are presented as means with SDs (p values from t tests), and categorical variables as counts with percentages (p values from $\chi^2$ or Fisher's tests). Time to first event or composite events were analysed using Poisson regression with robust SEs (at discharge from the hospital) or Cox proportional hazards models (at 30 days follow-up and 1 year follow-up), comparing the prasugrel-exposed group with the clopidogrel-exposed group. Risk ratios or HRs with 95% CIs are reported, respectively, both crude, and inverse propensity score estimators adjusted (using inverse-probability of treatment weight (IPTW), where treatment is prasugrel exposure. The propensity score was calculated using the following baseline variables including risk factors as described for the ACUITY/HORIZONS-AMI[19] and National Cardiovascular Data Registry (NCDR) bleeding risk scores:[20] age, gender, body weight, Body Mass Index; (BMI) history of diabetes, hypertension, hypercholesterolaemia, current smoking, CAD, cerebrovascular event, myocardial infarction, PCI, CABG, peripheral vascular disease; proton pump inhibitor, creatine-based estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula, leucocyte count, ACS type (unstable angina, non-STEMI, STEMI), Killip class IV, anaemia; and procedural aspects comprising CABG, heparin, low-molecular weight heparin, glycoprotein IIb/IIIa antagonists. Cox's regressions weighted by IPTW were used, using 20 data sets generated from multiple imputations (refer to supplement for details) of missing values generated with chained equations. The c-statistic was 0.8307 and the goodness of fit on 10 groups was $\chi^2$ 8.82, df=8, p=0.3577. Prespecified stratified analyses of clinical outcomes at 1 year were performed comparing low-risk patients (age <75 years and body weight ≥60 kg, and no history of stroke or TIA) versus high-risk patients (age ≥75 years, body weight <60 kg, or history of stroke or TIA) as described.[3] Safety analyses on the composite outcome of BARC 3, 4 or 5 bleeding events at 1 year were performed, again stratified within major subgroups. Continuity-corrected risk ratios with 95% CIs and p values from Fisher's tests are reported in case of zero events (interaction tests were approximated using Z-tests). All analyses were based on the initial exposure to prasugrel versus clopidogrel, that is, ignoring cross-overs in medication. All statistical analyses were performed with Stata V.13.1 (StataCorp, Texas, USA) and differences were considered significant at $\alpha$=0.05.

## RESULTS

### Adherence to current guidelines for the use of prasugrel

Among 2286 patients recruited into the Swiss ACS Bleeding Cohort, 138 patients were excluded as these patients received ticagrelor or were referred for CABG, resulting in a total of 2148 patients available for analysis (figure 1). Complete 30 day follow-up data were available for 98.8% of patients in the prasugrel group (747/756) and 99% of patients in the clopidogrel group (1378/1392). At 1 year, complete data were available for

**Table 2** Medication compliance at discharge, at 30 days follow-up and at 1 year follow-up

| Total number of patients | Prasugrel N=756 | Clopidogrel N=1392 | p Value |
|---|---|---|---|
| At discharge | n=750 | n=1368 | |
| Aspirin | 748 (99.7%) | 1355 (99.0%) | 0.102 |
| Clopidogrel | 37 (4.9%) | 1010 (73.8%) | <0.001 |
| Prasugrel | 703 (93.7%) | 217 (15.9%) | <0.001 |
| Any DAPT | 742 (98.9%) | 1232 (90.1%) | <0.001 |
| Statin | 745 (99.3%) | 1331 (97.4%) | 0.001 |
| ACE inhibitor | 637 (84.9%) | 989 (72.3%) | <0.001 |
| β-blocker | 631 (84.2%) | 1062 (77.7%) | <0.001 |
| Proton-pump inhibitor | 163 (21.7%) | 418 (30.6%) | <0.001 |
| NSAID | 18 (2.4%) | 14 (1.0%) | 0.016 |
| Immunosuppressives | 14* (2.1%) | 40† (3.0%) | 0.244 |
| At 30 days | n=733 | n=1336 | |
| Aspirin | 726 (99.0%) | 1310 (98.1%) | 0.099 |
| Clopidogrel | 64 (8.7%) | 962 (72.1%) | <0.001 |
| Prasugrel | 652 (88.9%) | 223 (16.7%) | <0.001 |
| Any DAPT | 713 (97.3%) | 1184 (88.6%) | <0.001 |
| Statin | 714 (97.4%) | 1279 (95.7%) | 0.066 |
| ACE inhibitor | 572 (78.0%) | 912 (68.3%) | <0.001 |
| β-blocker | 636 (86.8%) | 1098 (82.2%) | 0.007 |
| Proton-Pump Inhibitor | 151 (20.6%) | 400 (29.9%) | <0.001 |
| NSAID | 11 (1.5%) | 13 (1.0%) | 0.29 |
| Immunosuppressives | 10‡ (1.5%) | 36§ (2.8%) | 0.084 |
| At 1 year | n=711 | n=1261 | |
| Aspirin | 696 (97.9%) | 1215 (96.4%) | 0.059 |
| Clopidogrel | 72 (10.1%) | 802 (63.7%)¶ | <0.001 |
| Prasugrel | 579 (81.4%) | 212 (16.8%) | <0.001 |
| Any DAPT | 645 (90.7%) | 1004 (79.6%) | <0.001 |
| Statin | 671 (94.5%)** | 1164 (92.3%) | 0.065 |
| ACE inhibitor | 463 (65.2%)** | 706 (56.0%) | <0.001 |
| β-blocker | 572 (80.6%)** | 977 (77.5%) | 0.11 |
| Proton-pump inhibitor | 164 (23.1%)** | 357 (28.3%) | 0.012 |
| NSAID | 18 (2.5%)** | 17 (1.3%) | 0.074 |
| Immunosuppressives | 9 (1.4%)†† | 33 (2.7%)‡‡ | 0.073 |

Depicted are counts (%).
*N=681.
†N=1321.
‡N=664.
§N=1292.
¶N=1260.
**N=710.
††N=643
‡‡N=1219.
DAPT, dual-antiplatelet therapy (aspirin with clopidogrel, prasugrel or ticagrelor); NSAID, non-steroidal inflammatory drugs.

96.4% (729/756) inpatients receiving prasugrel and 95.8% (1334/1392) inpatients receiving clopidogrel. According to current guidelines for the use of prasugrel,[6 7] only 7.5% of patients were ≥75 years old, only 3.0% were <60 kg and only 1.3% had a prior history of stroke or TIA (table 1). Among patients in the clopidogrel group, 90.9% received a loading dose of clopidogrel (600 mg in 88.5% of patients, see online supplementary table S1) and 96.7% in the prasugrel group were loaded with prasugrel (60 mg in 87.6% of patients, see online supplementary table S2). Compliance at 30 days follow-up was

**Table 3** Bleeding events inhospital, at 30 days follow-up and at 1 year follow-up

| | Prasugrel | Clopidogrel | Crude | | IPTW adjusted | |
|---|---|---|---|---|---|---|
| Total number of patients | N=756 | N=1392 | HR or RR (95% CI) | p Value | HR or RR (95% CI) | p Value |
| Inhospital | | | | | | |
| TIMI | | | | | | |
| TIMI (major) | 10 (1.3) | 24 (1.7) | 0.77 (0.37 to 1.60) | 0.478 | 0.90 (0.39 to 2.08) | 0.813 |
| TIMI (major non-CABG related) | 8 (1.2) | 13 (1.0) | 1.21 (0.50 to 2.90) | 0.675 | 1.02 (0.40 to 2.55) | 0.974 |
| TIMI (minor) | 8 (1.1) | 23 (1.7) | 0.64 (0.29 to 1.43) | 0.275 | 0.64 (0.28 to 1.48) | 0.297 |
| TIMI (minimal) | 4 (0.5) | 25 (1.8) | 0.29 (0.10 to 0.84) | 0.023 | 0.23 (0.08 to 0.71) | 0.010 |
| GUSTO | | | | | | |
| GUSTO (severe or life-threatening) | 5 (0.7) | 17 (1.2) | 0.54 (0.20 to 1.46) | 0.226 | 0.77 (0.25 to 2.33) | 0.644 |
| GUSTO (moderate) | 3 (0.4) | 19 (1.4) | 0.29 (0.09 to 0.98) | 0.046 | 0.25 (0.07 to 0.87) | 0.029 |
| GUSTO (mild) | 14 (1.9) | 36 (2.6) | 0.72 (0.39 to 1.32) | 0.284 | 0.62 (0.32 to 1.18) | 0.148 |
| BARC | | | | | | |
| BARC (3,4,5) | 18 (2.4) | 48 (3.4) | 0.69 (0.40 to 1.18) | 0.174 | 0.75 (0.42 to 1.36) | 0.350 |
| BARC (5ab) | 2 (0.3) | 0 (0.0) | 9.20 (0.44 to 191.38) | 0.124 | | |
| BARC (4) | 1 (0.1) | 12 (0.9) | 0.15 (0.02 to 1.18) | 0.072 | 0.57 (0.07 to 4.35) | 0.585 |
| BARC (3abc) | 15 (2.0) | 37 (2.7) | 0.75 (0.41 to 1.35) | 0.334 | 0.66 (0.36 to 1.24) | 0.201 |
| At 30 days* | | | | | | |
| TIMI | | | | | | |
| TIMI (major) | 11 (1.5) | 29 (2.1) | 0.70 (0.35 to 1.39) | 0.304 | 0.78 (0.35 to 1.71) | 0.529 |
| TIMI (major non-CABG related) | 9 (1.3) | 16 (1.2) | 1.10 (0.49 to 2.49) | 0.817 | 0.86 (0.36 to 2.04) | 0.734 |
| TIMI (minor) | 8 (1.1) | 25 (1.8) | 0.59 (0.26 to 1.30) | 0.190 | 0.59 (0.26 to 1.36) | 0.215 |
| TIMI (minimal) | 4 (0.5) | 29 (2.1) | 0.25 (0.09 to 0.72) | 0.010 | 0.19 (0.06 to 0.58) | 0.003 |
| GUSTO | | | | | | |
| GUSTO (severe or life-threat.) | 5 (0.7) | 21 (1.5) | 0.44 (0.16 to 1.15) | 0.095 | 0.65 (0.22 to 1.93) | 0.440 |
| GUSTO (moderate) | 4 (0.5) | 22 (1.6) | 0.33 (0.11 to 0.96) | 0.043 | 0.27 (0.09 to 0.79) | 0.017 |
| GUSTO (mild) | 14 (1.9) | 41 (3.0) | 0.63 (0.34 to 1.15) | 0.130 | 0.53 (0.28 to 1.00) | 0.050 |
| BARC | | | | | | |
| BARC (3,4,5) | 19 (2.5) | 55 (4.0) | 0.63 (0.38 to 1.06) | 0.084 | 0.67 (0.38 to 1.20) | 0.181 |
| BARC (5ab) | 2 (0.3) | 0 (0.0) | 9.20 (0.44 to 191.38) | 0.124 | | |
| BARC (4) | 1 (0.1) | 15 (1.1) | 0.12 (0.02 to 0.92) | 0.041 | 0.46 (0.06 to 3.46) | 0.447 |
| BARC (3abc) | 16 (2.1) | 42 (3.0) | 0.70 (0.39 to 1.24) | 0.222 | 0.61 (0.33 to 1.11) | 0.104 |
| At 1 year* | | | | | | |
| TIMI | | | | | | |
| TIMI (major) | 20 (2.7) | 43 (3.2) | 0.84 (0.50 to 1.43) | 0.530 | 0.77 (0.42 to 1.41) | 0.396 |
| TIMI (major non-CABG related) | 17 (2.5) | 29 (2.3) | 1.14 (0.63 to 2.07) | 0.673 | 0.80 (0.42 to 1.54) | 0.510 |
| TIMI (minor) | 8 (1.1) | 31 (2.3) | 0.47 (0.22 to 1.02) | 0.057 | 0.45 (0.20 to 1.02) | 0.057 |
| TIMI (minimal) | 11 (1.5) | 57 (4.3) | 0.34 (0.18 to 0.66) | 0.001 | 0.43 (0.17 to 1.06) | 0.068 |
| GUSTO | | | | | | |
| GUSTO (severe or life-threat.) | 9 (1.2) | 31 (2.3) | 0.52 (0.25 to 1.10) | 0.089 | 0.59 (0.25 to 1.38) | 0.222 |
| GUSTO (moderate) | 9 (1.2) | 31 (2.3) | 0.53 (0.25 to 1.10) | 0.089 | 0.46 (0.21 to 1.03) | 0.058 |
| GUSTO (mild) | 21 (2.8) | 70 (5.3) | 0.54 (0.33 to 0.88) | 0.013 | 0.56 (0.30 to 1.06) | 0.073 |
| BARC | | | | | | |
| BARC (3,4,5) | 28 (3.8) | 74 (5.5) | 0.68 (0.44 to 1.06) | 0.088 | 0.63 (0.39 to 1.03) | 0.063 |
| BARC (5ab) | 2 (0.3) | 1 (0.1) | 3.65 (0.33 to 40.29) | 0.290 | 4.83 (0.43 to 54.24) | 0.202 |
| BARC (4) | 2 (0.3) | 15 (1.1) | 0.24 (0.06 to 1.06) | 0.060 | 0.55 (0.10 to 3.12) | 0.499 |
| BARC (3abc) | 24 (3.2) | 60 (4.5) | 0.73 (0.45 to 1.16) | 0.184 | 0.57 (0.34 to 0.95) | 0.032 |

Depicted are counts (% incidence at discharge). First event per bleeding criteria for each patient only.
All bleeding events were adjudicated for TIMI, GUSTO and BARC criteria, except one bleeding event with insufficient information.
Inhospital: Poisson regressions with robust error variances, reporting RRs with 95% CIs and p values; At 30 days and 1 year: Cox's regressions, reporting HRs with 95% CIs and p values. IPTW for the exposure to prasugrel adjusted estimates using 20 multiple imputed data sets.
*Censored patients at last contact date or death, and incidence rates from Kaplan-Meier estimates.
BARC, Bleeding Academic Research Consortium classification; CABG, coronary artery bypass graft; GUSTO, Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries classification; IPTW, inverse probability of treatment weight; RR, risk ratio; TIMI, Thrombolysis In Myocardial Infarction classification.

88.9% for patients treated with prasugrel and 72.1% for patients treated with clopidogrel. At 1 year, compliance was 81.4% in the prasugrel group and 63.7% in the clopidogrel group (table 2).

### Bleeding events

Clinically relevant bleeding events (adjusted composite of BARC type 3, 4 or 5 bleeding event) occurred at similar frequency in both groups at hospital discharge and follow-up at 30 days (table 3); at 1 year, a trend towards a reduction in bleeding events was noted comparing prasugrel-exposed patients with clopidogrel-exposed patients (adjusted HR 0.63, 95% CI 0.39 to 1.03, p=0.06). The incidence of the primary safety end point (BARC type 3, 4 and 5 bleeding events) during 1 year follow-up in major subgroups was similar (figure 2). Stratified analysis of patients by risk category with low bleeding risk defined as the absence of a history of stroke or TIA, age <75 years and body weight ≥60 kg or high-risk, respectively, showed no difference in outcome at 1 year follow-up for individual safety end points (figure 3). The anatomical distribution of bleeding events was similar among patients treated with prasugrel or clopidogrel at 30 days follow-up and 1 year follow-up (see online supplementary table S3). Most bleeding events occurring in the first 30 days after an ACS manifested at the vascular access site followed by retroperitoneal, genitourinary and gastrointestinal sites. No intracranial and intraocular bleeding events were observed. At 1 year, the vascular access site remained the prevailing location followed in descending frequency by gastrointestinal, genitourinary and retroperitoneal sites. We conducted sensitivity analyses in our cohort by adding the NCDR Bleeding Risk Score or estimated glomerular filtration rate to the IPTW Cox model. In addition, we performed sensitivity analyses after excluding patients who initially presented with clopidogrel and then received prasugrel. All these analyses showed no difference (see online supplementary table S4) in clinically relevant bleeding events (BARC type 3, 4 and 5 bleeding).

### Major adverse cardiovascular and cerebrovascular events

After adjustment for baseline variables, no differences in MACCE (death, reinfarction, revascularisation, cerebrovascular events and definite stent thrombosis) at hospital discharge and

| Total nr. of patients | Prasugrel events/n n = 756 | Clopidogrel events/n n = 1392 | IPTW HR (95% CI) | p-value | p-value interaction |
|---|---|---|---|---|---|
| Age ≥75 years | | | | | 0.944 |
| Yes | 4/57 | 27/409 | 0.69 (0.22-2.15) | 0.521 | |
| No | 24/699 | 47/983 | 0.66 (0.38-1.15) | 0.141 | |
| Gender | | | | | 0.303 |
| Male | 18/639 | 49/1054 | 0.53 (0.30-0.96) | 0.036 | |
| Female | 10/117 | 25/338 | 0.93 (0.40-2.15) | 0.868 | |
| Weight <60 kg | | | | | 0.476 |
| Yes | 2/22 | 14/102 | 0.38 (0.07-2.11) | 0.267 | |
| No | 26/720 | 60/1269 | 0.70 (0.42-1.18) | 0.178 | |
| History of Stroke or TIA | | | | | 0.858 |
| Yes | 0/10 | 5/67 | 0.58 (0.03-9.74) | 1.000 | |
| No | 28/746 | 69/1325 | 0.65 (0.40-1.07) | 0.090 | |
| Diabetes mellitus | | | | | 0.474 |
| Yes | 1/107 | 18/276 | 0.34 (0.04-2.52) | 0.289 | |
| No | 27/649 | 56/1116 | 0.71 (0.43-1.17) | 0.174 | |
| Hypertension | | | | | 0.198 |
| Yes | 11/360 | 51/871 | 0.47 (0.23-0.99) | 0.048 | |
| No | 17/396 | 23/521 | 0.91 (0.46-1.80) | 0.786 | |
| Hypercholesterolaemia | | | | | 0.371 |
| Yes | 12/412 | 42/893 | 0.50 (0.24-1.06) | 0.071 | |
| No | 16/342 | 32/496 | 0.79 (0.41-1.53) | 0.491 | |
| ACS[a] | | | | | 0.151 |
| STEMI | 28/662 | 35/580 | 1.00 (0.58-1.72) | 0.998 | |
| NSTEMI | 0/85 | 38/741 | 0.11 (0.01-1.77) | 0.026 | |
| PPI at baseline | | | | | 0.943 |
| Yes | 3/78 | 14/233 | 0.66 (0.18-2.41) | 0.527 | |
| No | 25/671 | 60/1152 | 0.63 (0.37-1.07) | 0.086 | |
| Glycoprotein IIb/IIIa antagonists at procedure | | | | | 0.522 |
| Yes | 10/242 | 24/382 | 0.51 (0.23-1.13) | 0.098 | |
| No | 18/513 | 50/1010 | 0.71 (0.38-1.31) | 0.267 | |

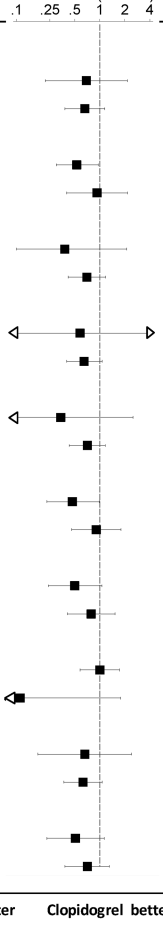


**Figure 2** Inverse-probability of treatment weight (IPTW)-adjusted analyses on Bleeding Academic Research Consortium (BARC) 3, 4 or 5 bleeding events at 1 year of follow-up for subgroups according to baseline characteristics. Depicted are events/total numbers of patients and only first event per outcome for each patient. NA=not available. Safety BARC: first occurrence of a BARC 3, 4 or 5 bleeding event. Censored patients at last contact date or death. Cox regressions reported IPTW-adjusted HRs with 95% CIs and p values. Risk ratios with continuity correction in case of zero events. [a]Patients with unstable angina (n=9 prasugrel; n=69 clopidogrel) only experienced one BARC 3, 4 or 5 type bleeding event in a clopidogrel-exposed patient. [b]Z-test on log-transformed estimates of the difference in ratios. IPTW, inverse-probability of treatment weighing; BARC, Bleeding Academic Research Consortium; TIA, transient ischaemic attack; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; PPI, proton pump inhibitor.

30 days follow-up were demonstrated comparing patients treated with prasugrel or clopidogrel, respectively (table 4). At 1 year, patients treated with prasugrel had a lower rate of all-cause death compared with patients receiving clopidogrel (adjusted HR 0.49, 95% CI 0.29 to 0.84, p=0.009; table 4). This difference coincided with an increased number of non-cardiovascular deaths in clopidogrel-treated patients (see online supplementary table S5).

## DISCUSSION

This is the first large real-world prospective study outside of the randomised controlled TRITON-TIMI 38 trial to report long-term outcome data for patients treated with prasugrel or clopidogrel in a multicentre cohort of patients with ACS referred for coronary angiography. Our study demonstrates a similar safety profile of prasugrel and clopidogrel with respect to clinically relevant bleeding events up to 1 year after ACS in patients treated according to current guideline recommendations.

Our ACS Bleeding Cohort constitutes a prospective cohort enrolling patients with ACS referred for coronary angiography recruited at four tertiary centres across Switzerland. During enrolment, prasugrel was available at all centres following approval by the Swiss regulatory authority and approved for reimbursement by insurance companies. Prasugrel or clopidogrel were administered to patients at the discretion of the treating cardiologist with a recommendation to use prasugrel in patients with STEMI based on the TRITON-TIMI 38 analysis of patients with STEMI.[5] Strict adherence to guidelines[6 7] as detailed in the prescribing information for the use of prasugrel in patients with ACS is reflected by a very rare use in patients receiving prasugrel with a history of stroke or TIA (1.3%) and in patients with advanced age (≥75 years; 7.5%) or low body weight (<60 kg; 3.0%). The majority of patients received the usual dosages of prasugrel or clopidogrel for loading (60 mg or 600 mg, respectively), as recommended by current guidelines.[6 7] Bleeding events were graded using the TIMI,[14] GUSTO[15] and novel BARC classifications.[16]

Clinically relevant bleeding events (BARC type 3, 4 or 5) were not different between patients treated with prasugrel or clopidogrel. Our data are in contrast to the TRITON-TIMI 38 trial which found an excess of serious bleeding events in patients receiving prasugrel compared with clopidogrel[3] but similar to the TRILOGY trial where patients were managed non-invasively.[21] Interestingly, a subgroup analysis of patients with STEMI from the TRITON-TIMI 38 study found no difference in non-CABG-related bleeding rates between prasugrel and clopidogrel,[5] corroborating the findings from our cohort with a predominance of patients with STEMI (58% in the entire cohort). In our cohort, 88% of patients with STEMI were treated with prasugrel, whereas 42% were treated with clopidogrel. Thus, this comparison deserves caution.

Subgroup analyses in our Swiss ACS Bleeding Cohort with respect to the primary safety end point at 1 year (BARC type 3, 4 or 5 bleeding) including STEMI as a separate group (figure 2) showed no difference in bleeding rates. Moreover, in our cohort bleeding events of BARC type 3, 4 or 5 occurred at a similar rate in both treatment groups when analysing high-risk and low-risk patients.

A subgroup analysis of TRITON-TIMI 38 identified a set of predictors of serious bleeding events comprising female gender, use of glycoprotein IIb/IIIa inhibitor, duration of intervention, age, assignment to prasugrel, regional characteristics, admission diagnosis of STEMI, femoral access for angiography, creatine clearance, hypercholesterolaemia and arterial hypertension.[22] In our Swiss ACS Bleeding Cohort, glycoprotein IIb/IIIa inhibitors were less frequently used (29%) than in TRITON-TIMI 38 (55%)[3] which may contribute to the observed low bleeding rate in our study. Finally, the incidence of clinically relevant bleeding

| Total nr. of patients | Prasugrel events/N N = 756 | Clopidogrel events/N N = 1392 | IPTW HR (95% CI) | p-value | p-value interaction |
|---|---|---|---|---|---|
| BARC Bleeding (3,4,5) | | | | | 0.439 |
| Low Risk | 23/677 | 37/915 | 0.78 (0.43-1.40) | 0.402 | |
| High Risk | 5/79 | 37/477 | 0.49 (0.17-1.38) | 0.175 | |
| TIMI (major or minor) | | | | | 0.431 |
| Low Risk | 23/677 | 36/915 | 0.81 (0.45-1.46) | 0.487 | |
| High Risk | 5/79 | 36/477 | 0.50 (0.18-1.42) | 0.195 | |
| TIMI (major) | | | | | 0.827 |
| Low Risk | 16/677 | 23/915 | 0.87 (0.42-1.81) | 0.704 | |
| High Risk | 4/79 | 20/477 | 0.74 (0.23-2.41) | 0.620 | |
| TIMI (major non-CABG related) | | | | | 0.659 |
| Low Risk | 13/677 | 16/915 | 0.78 (0.36-1.73) | 0.547 | |
| High Risk | 4/79 | 13/477 | 1.09 (0.32-3.73) | 0.890 | |
| GUSTO (severe or life-threatening) | | | | | 0.292 |
| Low Risk | 8/677 | 15/915 | 0.84 (0.31-2.24) | 0.721 | |
| High Risk | 1/79 | 16/477 | 0.24 (0.03-1.93) | 0.182 | |

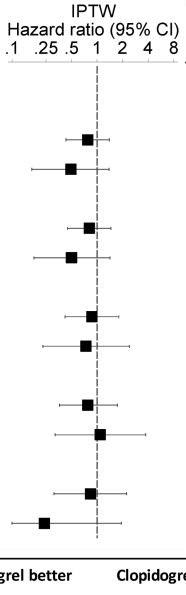


**Figure 3** Stratified inverse-probability of treatment weight (IPTW)-adjusted analyses of bleeding events at 1 year of follow-up for low-risk and high-risk patients. Depicted are events/total numbers of patients. Low-risk assumed for n=24 patients with weight missing (12 prasugrel, 10 clopidogrel). All 24 patients were without history of stroke or transient ischaemic attack (TIA) and <75 years of age, this was the first event per outcome for each patient only. Cox regressions reported IPTW-adjusted HRs with 95% CIs and p values. IPTW, inverse-probability of treatment weighing; BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis In Myocardial Infarction; GUSTO, Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries.

**Table 4** Clinical outcomes inhospital, at 30 days follow-up and at 1 year follow-up

| Total number of patients | Prasugrel N=756 | Clopidogrel N=1392 | Crude HR or RR (95% CI) | Crude p Value | IPTW adjusted HR or RR (95% CI) | IPTW adjusted p Value |
|---|---|---|---|---|---|---|
| Inhospital | | | | | | |
| Death | 5 (0.7) | 26 (1.9) | 0.35 (0.14 to 0.92) | 0.033 | 0.41 (0.15 to 1.09) | 0.074 |
| Cardiac death | 4 (0.5) | 26 (1.9) | 0.28 (0.10 to 0.81) | 0.018 | 0.35 (0.12 to 1.03) | 0.058 |
| Reinfarction (any) | 7 (0.9) | 12 (0.9) | 1.07 (0.42 to 2.72) | 0.880 | 2.69 (0.90 to 8.01) | 0.075 |
| Revascularisation (any) | 7 (0.9) | 12 (0.9) | 1.07 (0.42 to 2.72) | 0.880 | 2.08 (0.64 to 6.76) | 0.223 |
| Revascularisation (ischaemia-driven) | 7 (0.9) | 10 (0.7) | 1.29 (0.49 to 3.37) | 0.605 | 2.49 (0.74 to 8.35) | 0.140 |
| Cerebrovascular events (any) | 3 (0.4) | 9 (0.6) | 0.61 (0.17 to 2.26) | 0.463 | 1.07 (0.26 to 4.40) | 0.927 |
| Stroke (any) | 2 (0.3) | 8 (0.6) | 0.46 (0.10 to 2.16) | 0.326 | 0.92 (0.18 to 4.75) | 0.918 |
| Ischaemic stroke | 2 (0.3) | 7 (0.5) | 0.53 (0.11 to 2.53) | 0.422 | 1.04 (0.20 to 5.53) | 0.965 |
| Intracerebral haemorrhage | 0 (0.0) | 0 (0.0) | | | | |
| Unclear aetiology | 0 (0.0) | 1 (0.1) | 0.61 (0.02 to 14.96) | 1.000 | | |
| TIA | 1 (0.1) | 1 (0.1) | 1.84 (0.12 to 29.41) | 0.666 | 2.80 (0.18 to 44.88) | 0.466 |
| Definite stent thrombosis | 4 (0.5) | 5 (0.4) | 1.47 (0.40 to 5.47) | 0.563 | 3.02 (0.62 to 14.64) | 0.170 |
| At 30 days* | | | | | | |
| Death | 11 (1.5) | 37 (2.7) | 0.54 (0.28 to 1.07) | 0.077 | 0.60 (0.30 to 1.22) | 0.157 |
| Cardiac death | 10 (1.3) | 34 (2.4) | 0.54 (0.27 to 1.09) | 0.086 | 0.62 (0.30 to 1.28) | 0.194 |
| Reinfarction (any) | 9 (1.2) | 19 (1.4) | 0.87 (0.39 to 1.92) | 0.728 | 1.82 (0.68 to 4.85) | 0.231 |
| Revascularisation (any) | 14 (1.9) | 25 (1.8) | 1.03 (0.53 to 1.97) | 0.939 | 1.32 (0.55 to 3.20) | 0.535 |
| Revascularisation (ischaemia-driven) | 14 (1.9) | 22 (1.6) | 1.17 (0.60 to 2.28) | 0.651 | 1.55 (0.63 to 3.80) | 0.335 |
| Cerebrovascular events (any) | 5 (0.7) | 12 (0.9) | 0.76 (0.27 to 2.16) | 0.611 | 1.16 (0.37 to 3.64) | 0.803 |
| Stroke (any) | 4 (0.5) | 10 (0.7) | 0.73 (0.23 to 2.33) | 0.598 | 1.15 (0.32 to 4.14) | 0.827 |
| Ischaemic stroke | 4 (0.5) | 9 (0.7) | 0.81 (0.25 to 2.64) | 0.731 | 1.28 (0.35 to 4.69) | 0.711 |
| Intracerebral haemorrhage | 0 (0.0) | 0 (0.0) | | | | |
| Unclear aetiology | 0 (0.0) | 1 (0.1) | 0.61 (0.02 to 14.96) | 1.000 | | |
| TIA | 1 (0.1) | 2 (0.1) | 0.92 (0.08 to 10.11) | 0.943 | 1.18 (0.11 to 13.18) | 0.892 |
| Definite stent thrombosis | 6 (0.8) | 10 (0.7) | 1.10 (0.40 to 3.03) | 0.852 | 1.68 (0.45 to 6.30) | 0.442 |
| At 1 year* | | | | | | |
| Death | 20 (2.7) | 74 (5.4) | 0.49 (0.30 to 0.80) | 0.005 | 0.49 (0.29 to 0.84) | 0.009 |
| Cardiac death | 19 (2.6) | 57 (4.2) | 0.61 (0.36 to 1.02) | 0.058 | 0.62 (0.35 to 1.08) | 0.090 |
| Reinfarction (any) | 20 (2.7) | 50 (3.8) | 0.72 (0.43 to 1.21) | 0.218 | 1.40 (0.70 to 2.80) | 0.337 |
| Revascularisation (any) | 43 (5.9) | 88 (6.7) | 0.88 (0.61 to 1.27) | 0.491 | 1.09 (0.65 to 1.82) | 0.746 |
| Revascularisation ( ischaemia-driven) | 42 (5.8) | 81 (6.2) | 0.93 (0.64 to 1.36) | 0.720 | 1.17 (0.69 to 1.97) | 0.558 |
| Cerebrovascular events (any) | 9 (1.2) | 28 (2.1) | 0.58 (0.27 to 1.23) | 0.156 | 0.96 (0.42 to 2.20) | 0.921 |
| Stroke (any) | 7 (1.0) | 21 (1.6) | 0.60 (0.26 to 1.42) | 0.246 | 0.92 (0.36 to 2.38) | 0.863 |
| Ischaemic stroke | 7 (1.0) | 17 (1.3) | 0.75 (0.31 to 1.80) | 0.514 | 1.20 (0.45 to 3.17) | 0.719 |
| Intracerebral haemorrhage | 0 (0.0) | 3 (0.2) | 0.26 (0.01 to 5.03) | 0.556 | | |
| Unclear aetiology | 0 (0.0) | 1 (0.1) | 0.61 (0.02 to 14.96) | 1.000 | | |
| TIA | 2 (0.3) | 8 (0.6) | 0.45 (0.10 to 2.13) | 0.314 | 0.96 (0.18 to 5.02) | 0.964 |
| Definite stent thrombosis | 8 (1.1) | 13 (1.0) | 1.12 (0.47 to 2.71) | 0.797 | 1.39 (0.42 to 4.64) | 0.591 |

Depicted are counts (% incidence at discharge, % incidence at follow-up 30 days from life tables with censoring at last contact date). First event per outcome for each patient only.
*Censored patients at last contact date or death, and incidence rates from Kaplan-Meier estimates.
Inhospital: Poisson regressions with robust error variances, reporting RRs with 95% CIs and p values; At 30 days and 1 year: Cox's regressions, reporting HRs with 95% CIs and p values. RR with continuity correction in case of zero events. IPTW for the exposure to prasugrel adjusted estimates using 20 multiple imputed data sets.
IPTW, inverse probability of treatment weight; RR, risk ratio; TIA, transient ischaemic attack.

events demonstrated in our Swiss ACS Bleeding Cohort is consistent with published data on novel inhibitors of platelet aggregation as demonstrated by the ACCOAST,[23] TRITON-TIMI 38,[3] TRILOGY ACS,[21] PLATO[24] and CHAMPION PHOENIX[25] trials (table 5) which makes under-reporting of events in our cohort very unlikely.

Adjusted analyses of MACCE showed no difference at any of the three time points (hospital discharge, follow-up at 30 days and follow-up at 1 year). There was, however, a trend towards cardiac death reduction with prasugrel at 1 year. This decrease in the number of observed all-cause deaths is interesting in that it does not reflect the outcome in the TRITON-TIMI 38 trial[3] which found the main benefit for prasugrel with respect to a reduction in recurrence of non-fatal myocardial infarction with no effect on cardiovascular mortality and non-fatal stroke forming the three constituents of the primary end point.

Our findings need to be appreciated in light of (1) variation in treatment effects for prasugrel which depend on patient characteristics (ie, patients with STEMI are younger with less comorbidity),[26] (2) adherence to the recommended use of prasugrel with avoidance or reduced dosing of prasugrel in patients with high bleeding risk yielding older individuals in the clopidogrel group,[3 6 7] (3) low patient numbers and low bleeding rates compared with TRITON-TIMI 38,[3] thus limiting statistical power, (4) a frequent use of a higher loading dose of clopidogrel (600 mg) in our cohort unlike in TRITON-TIMI 38 (300 mg).

**Table 5** Bleeding with novel inhibitors of platelet aggregation in ACS

| Study | Year | Patients | Drugs and patient setting | Common safety end point, outcome |
|---|---|---|---|---|
| **Swiss ACS Bleeding Cohort** | 2014 | 2148 | Prasugrel or clopidogrel, ACS, invasive management | Non-CABG-related TIMI major bleeding at 30 days, 1.3% vs 1.2% (HR 0.86, 95% CI 0.36 to 2.04, p=0.7) |
| **ACCOAST** | 2013 | 4033 | Prasugrel pretreatment vs prasugrel no pretreatment, NSTEMI, invasive management | Non-CABG-related TIMI major bleeding at 30 days, 1.6% vs 0.6% (HR 2.86, 95% CI 1.44 to 5.68, p=0.002) |
| **TRITON-TIMI 38** | 2007 | 13 608 | Prasugrel vs cllopidogrel, ACS, invasive management | Non-CABG-related TIMI major bleeding at 15 m, 2.4% vs 1.8% (HR 1.32, 95% CI 1.03 to 1.68, p=0.03) |
| **TRILOGY ACS** | 2012 | 7243 | Prasugrel vs clopidogrel, ACS (<75 years), medical management | Non-CABG-related TIMI major bleeding at 30 m, 2.1% vs 1.5% (HR 1.31, 95% CI 0.81 to 2.11, p=0.27) |
| **PLATO** | 2009 | 18 624 | Ticagrelor vs clopidogrel, ACS, invasive/medical management (60.9%) | Non-CABG-related TIMI major bleeding at 12 m, 2.8% vs 2.2% (HR 1.25, 95% CI 1.03 to 1.53, p=0.03) |
| **CHAMPION PHOENIX** | 2013 | 11 145 | Cangrelor vs clopidogrel, stable angina, ACS, invasive management | Non-CABG-related TIMI major bleeding at 48 h, 0.1% vs 0.1% (HR 1.00, 95% CI 0.29 to 3.45, p>0.9) |

ACS, acute coronary syndromes; CABG, coronary artery bypass graft; NSTEMI, non-ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

A separate study showed that increased clopidogrel loading was associated with a reduced MACCE rate without an increase in major bleeding events in patients with ACS.[27]

### Limitations

Application of the label recommendations for prasugrel based on the results of the TRITON-TIMI 38 trial, in particular the age limit of 75 years, resulted in differences in characteristics of patients receiving prasugrel versus patients receiving clopidogrel. This makes the comparison between treatment groups difficult, but reflects current guidelines. We used IPTW for statistical adjustment of estimates, but this may have been only partially successful because of incomplete ascertainment of relevant patient characteristics such as history of previous bleeding episodes and compliance with medication including switching of medications. As per design of this prospective cohort, utmost attention was taken to provide consistent reporting of events.

### Key messages

**What is already known on this subject?**

Prasugrel inhibits platelet aggregation more rapidly than clopidogrel. In patients with acute coronary syndromes (ACS), the TRial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet InhibitioN with Prasugrel—Thrombolysis In Myocardial Infarction 38 showed a benefit in terms of major adverse cardiovascular events at the expense of an increase in serious bleeding of prasugrel versus clopidogrel. However, the study revealed a safety concern in prasugrel-treated patients with a history of stroke or transient ischaemic attack, age ≥75 years or weight <60 kg.

**What might this study add?**

This study provides real-world evidence in a prospective, large Swiss multicentre cohort about safety of prasugrel and clopidogrel. Thirty days after ACS, clinically relevant bleeding events occurred in 2.5% of patients on prasugrel and in 4.0% of patients on clopidogrel if used according to current guidelines (ie, in patients with a history of stroke or transient ischaemic attack, age ≥75 years or weight <60 kg). We report safety data using the novel Bleeding Academic Research Consortium classification in addition to the common Thrombolysis In Myocardial Infarction and Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries criteria.

**How might this impact on clinical practice?**

Our study shows that prasugrel is safe in real-world ACS-percutaneous coronary intervention patients if used according to guidelines.

### Conclusions

Our large, prospective cohort study documents real-world outcome data on prasugrel and clopidogrel in patients with ACS treated according to current guidelines. Patients with ACS-PCI on prasugrel had no increase in clinically relevant bleeding events. We report safety data for prasugrel and clopidogrel using the novel BARC classification in addition to the common TIMI and GUSTO classifications. Our study demonstrates that prasugrel treatment used in everyday practice according to label instructions is safe in patients with ACS-PCI and thus, may complement the TRITON-TIMI 38 trial in this respect.[3] Given differences in characteristics of patients receiving prasugrel versus clopidogrel, low patient numbers and low bleeding rates compared with TRITON-TIMI 38,[3] our findings need to be replicated in larger samples.

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**Acknowledgements** The authors thank the clinical event committee for SPUM ACS for their work: Matthias Pfisterer, MD, Tiziano Moccetti, MD, Lukas Kappenberger, MD, Switzerland; and COMFORTABLE AMI Pascal Vranckx, MD, Belgium, Gerrit Hellige, MD, Switzerland, Igal Moarof, MD, Switzerland. The authors also thank the local study nurses (Anika Lewandowski, Maja Müller, Christa Schönenberger, Therese Fahrni, Saskia Bühlmann, Geneviève Legault, Véronique Berset, Nicole Bonvin, Anne Bevand, Amélie Delort), the central data monitors (Katja Heinimann, Daria Bochenek, Timon Spörri), the electronic data capturing system (2mt GmbH Ulm, Jürgen Nagler-Ihlein, Torsten Illmann), the research coordinator Lambertus J van Tits, PhD and the members of the local catheter teams.

**Funding** The authors received support from the Swiss National Science Foundation (SPUM 33CM30-124112); the Swiss Heart Foundation; the Fondation Leducq and

the Foundation for Cardiovascular Research, Zurich. The SPUM consortium was supported by Eli Lilly (USA), AstraZeneca, Roche, Medtronic, MSD, Sanofi, St Jude Medical (all Switzerland). The COMFORTABLE AMI study was supported by an unrestricted grant from Biosensors (Switzerland).

**Competing interests** RK received lecture fees from Eli Lilly, Servier and Bayer. MR received lecture and consultant fees from Daiichi-Sankyo, Eli Lilly and AstraZeneca. CTU Bern has a staff policy of not accepting honoraria or consultancy fees. P Jüni is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic and St Jude Medical. BM has received research grants to the institution form Abbott, Boston Scientific, Biosensors, and Cordis. FM has received research grants to the institution from Amgen, AstraZeneca, Boston Scientific, Biotronik, Medtronic, MSD, Eli Lilly and St Jude Medical including speaker or consultant fees. SW has received research grants to the institution from Abbott, AstraZeneca, Boston Scientific, Biosensors, Biotronik, Cordis, Eli Lilly, Medtronic and St Jude Medical. TFL received research grants to the institution from AstraZeneca, Bayer, Biosensors, Biotronik, Boston Scientific, Medtronic, MSD, Roche and Servier, including lecture fees. CMM received research grants to the institution from Eli Lilly, AstraZeneca, Roche and MSD. All other authors have no conflict of interest to declare.

**Patient consent** Obtained.

**Ethics approval** Cantonal Ethics Committees for Bern, Geneva, Lausanne and Zurich.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Data sharing of additional unpublished data from the study is available on request to the corresponding author.

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