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Rozprawa Doktorska

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„Wpływ stosowania przedoperacyjnego kwasu acetylosalicylowego na przebieg śród – i pooperacyjny u pacjentów poddawanych rewaskularyzacji”

w formie spójnego tematycznie cyklu artykułów opublikowanych w czasopismach naukowych

Promotor

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SPIS TREŚCI

Wykaz skrótów

ASA – Kwas acetylosalicylowy (acetylsalicylic acid)

CABG – Chirurgiczna rewaskularyzacja naczyń wieńcowych (Coronary Artery Bypass Grafting)

AKI – Ostre uszkodzenie nerek (Acute Kidney Injury)

CPB – Krążenie pozaustrojowe (Cardiopulmonary bypass)

COX - Cyklooksygenaza (Cyclooxygenase)

KDIGO – Kidney Disease Improving Global Outcomes

eGFR- Współczynnik przesączania kłębuszkowego (Estimated Glomerular Filtration Rate)

MDRD - Modification of Diet in Renal Disease formula

pRBC - Koncentrat krwinek czerwonych (Packed Red Blood Cell)

OR – Iloraz szans (Odds Ratio)

MD – Średnia różnica (Mean difference)

MACCE- Niepożądane zdarzenia sercowo-mózgowe (Major adverse cardiac and cerebral events)

OPCAB - Chirurgiczna rewaskularyzacja naczyń wieńcowych bez użycia krążenia pozaustrojowego (Off-pump coronary artery bypass grafting)

Cykl publikacji będący podstawą rozprawy doktorskiej

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„Wpływ stosowania przedoperacyjnego kwasu acetylosalicylowego na przebieg śród – i pooperacyjny u pacjentów poddawanych rewaskularyzacji”

A.1 Sleiman Sebastian Aboul-Hassan, Jakub Marczak, Tomasz Stankowski, Maciej Peksa, Marcin Nawotka, Ryszard Stanislawski, Romuald Cichon. Association Between Preoperative Aspirin And Acute Kidney Injury Following Coronary Artery Bypass Grafting. J Thorac Cardiovasc Surg. 2019. 2019 Sep 25. doi: 10.1016/j.jtcvs.2019.08.119. [Epub ahead of print]
(IF = 5.261, Pkt. MNiSW/KBN: 140.000)

A.2 Sleiman Sebastian Aboul-Hassan, Tomasz Stankowski, Maciej Peksa, Marcin Nawotka, Ryszard Stanislawski, Romuald Cichon. Timing Strategy of Preoperative Aspirin and Its Impact on Early Outcomes in Patients Undergoing Coronary Artery Bypass Grafting: A Propensity Score Matching Analysis. J Surg Res. 2019 Oct 11;246:251-259. doi: 10.1016/j.jss.2019.09.026. [Epub ahead of print].
(IF = 1.872, Pkt. MNiSW/KBN: 70.000)

A.3 Sleiman Sebastian Aboul-Hassan, Tomasz Stankowski, Maciej Peksa, Marcin Nawotka, Ryszard Stanislawski, Bartosz Kryszkowski, Romuald Cichon. The use of preoperative aspirin in cardiac surgery: A systematic review and meta-analysis. J Card Surg. 2017 Dec;32(12):758-774. doi: 10.1111/jocs.13250.
(IF = 1.179, Pkt. MNiSW/KBN: 20.000)

Rozdział I

STRESZCZENIE W WERSJI POLSKIEJ

Wstęp

Kwas acetylosalicylowy (ASA) jest jednym z podstawowych leków stosowanych u pacjentów z chorobą niedokrwienną serca. Główną zaletą stosowania ASA jest istotna skuteczność leku w prewencji pierwotnej oraz wtórnej chorób układu sercowo-naczyniowego. Zastosowanie ASA w ciągu 48 godzin po chirurgicznej rewaskularyzacji naczyń wieńcowych (CABG) jest związane ze znaczącym zmniejszeniem śmiertelności pooperacyjnej oraz ze zmniejszeniem częstotliwości występowania incydentów sercowo-naczyniowych. Ponadto, ASA istotnie zmniejszyła ryzyko zamknięcia żylnego przeszczepu naczyniowego, gdy podano pierwszą dawkę po CABG w ciągu 6 godzin. Pomimo znanych korzyści stosowania ASA u pacjentów po chirurgicznej rewaskularyzacji naczyń wieńcowych, kontynuacja lub wdrożenie terapii z ASA przed zabiegiem jest wciąż kontrowersyjne. Według wytycznych z 2017r. europejskiego towarzystwa kardio-torakochirurgicznego (EACTS- European Association of Cardio-Thoracic Surgery) dotyczących leczenia okołooperacyjnego u pacjentów poddanych zabiegom kardiochirurgicznym stwierdzono, że kontynuacja podawania ASA do czasu CABG powinna być wzięta pod uwagę (klasa IIa). Natomiast, wytyczne STS (The Society of Thoracic Surgeon) z 2012 r. dotyczące leczenia przeciwpłytkowego u pacjentów poddanych zabiegom kardio- oraz niekardiochirurgicznym zalecają przerwanie stosowanie ASA przed planowym zabiegiem w celu zmniejszenia ryzyka krwawienia pooperacyjnego. W związku z tym, do dziś kontynuacja lub wdrożenie terapii z ASA przed zabiegiem jest wciąż kontrowersyjne i

pozostawione według preferencji chirurga. Wielu chirurgów kontynuuje podaż ASA do dnia operacji, inni odstawiają kilka dni przed w celu zmniejszenia ryzyka krwawienia pooperacyjnego.

Powszechnie sądzi się, że pacjenci poddani CABG mają zwiększone ryzyko zdarzeń zakrzepowo-zatorowych wskutek indukowanej kaskady zapalnej oraz uszkodzenia śródbłonka naczyń związanego z użyciem krążenia pozaustrojowego. Natomiast u pacjentów operowanych bez użycia krążenia pozaustrojowego ryzyko zdarzeń zakrzepowo-zatorowych wciąż jest podwyższone, ponieważ zaobserwowano fenomen nadreaktywności płytek krwi oraz stan hiperkoagulopatii. Z drugiej strony, ostre uszkodzenie nerek (AKI) jest jednym z najczęstszych powikłań po operacjach kardiochirurgicznych. Według badań, AKI występuje u około 43% pacjentów po operacjach kardiochirurgicznych i wykazano, że wystąpienie AKI nawet pierwszego stopnia w okresie pooperacyjnym wpływa negatywnie na długoletnią przeżywalność tych pacjentów. Wiele czynników wpływa na ryzyko wystąpienia AKI po operacjach kardiochirurgicznych. Wśród czynników niemodyfikowalnych są: wiek, nadciśnienie, cukrzyca oraz choroba naczyń obwodowych. Natomiast krążenia pozaustrojowe, transfuzja substancji krwiopochodnych, leki podawane przed jak i śródoperacyjnie są czynnikami modyfikalnymi wpływającymi na zwiększone ryzyko wystąpienia AKI.

W związku z działaniem przeciwpłytkowym oraz przeciwzapalnym, zastosowanie ASA w okresie okołooperacyjnym może być odpowiedzialne za zmniejszenie ryzyka wczesnych pooperacyjnych incydentów zakrzepowo-zatorowych jak również za zmniejszenie ryzyka wystąpienia AKI w okresie pooperacyjnym. Meta-analiza przeprowadzona przez nasz zespół, która zbadała efekt działania przedoperacyjnego zastosowania ASA u pacjentów poddanych zabiegom kardiochirurgicznym pokazała, że przedoperacyjne zastosowanie ASA istotnie statystycznie zmniejsza trzydziestodniową śmiertelność, ilość zawałów śródoperacyjnych i

wystąpienie ostrego uszkodzenia nerek w okresie pooperacyjnym. Wyniki tej meta-analizy wykazały również, że kontynuacja ASA do czasu zabiegu zwiększa ryzyko istotnego krwawienia pooperacyjnego, jednak bez zwiększenia zapotrzebowania na przetoczenie koncentratów krwinek czerwonych. Podanie tego preparatu w opisywanym doniesieniu nie zwiększa również ryzyko reoperacji z powodu krwawienia, gdy zastosowano dawkę ASA w okresie przedoperacyjnym mniejszą niż 160 mg/dobę. Działanie przeciwzapalne ASA zachodzi przez wpływ na komórki śródbłonka naczyń, leukocyty i płytki krwi. ASA nieodwracalnie hamuje cykloksygenazy: 1- (COX-1) oraz 2 (COX-2). Płytkowe cyklooksygenazy są odpowiedzialne za produkcje Tromboksanu A_2, który jest głównym mediatorem agregacji płytek. Poprzez nieodwracalny wpływ na COX, czas działania ASA jest równy czasowi ponownej syntezy COX. Płytki krwi nie mają możliwości regulacji stężenia i aktywności COX, raz zahamowane pozostają nieaktywne aż do ich wymiany, czyli około siedmiu dni. Natomiast komórki śródbłonka naczyń mają możliwość regulacji ponownej syntezy COX z powodu zachowanego jądra komórkowego, dlatego po zastosowaniu ASA komórki śródbłonka naczyń potrzebują kilku godzin, aby ponownie aktywować działanie COX. Ostatnie doniesienia, wbrew powszechnemu przekonaniu wykazały, że po odstawieniu ASA, funkcja płytek stopniowo się normalizowała w ciągu 72 godzin uzyskując pełną funkcję 96 godzin po odstawieniu. Dlatego odstawienie ASA kilka dni przed CABG likwiduje efekt przeciwzapalny leku oraz może częściowo, jeśli nie całkowicie spowodować przywrócenie funkcji płytek zwiększając przy tym ryzyko zakrzepowo-zatorowe w okresie okołooperacyjnym. W związku z tym, kontynuacja ASA do czasu operacji, hipotetycznie, może zmniejszyć ryzyko wystąpień niepożądanych incydentów sercowo-naczyniowych. Hipotezę tą potwierdza badanie wykonane przez Deng i wsp. gdzie wykazano, że kontynuacja podawania ASA do 24 godz. przed zabiegiem związana była ze znaczną mniejszą śmiertelnością 30-dniową w porównaniu do ASA podawanej 24 do 72 godz. przed CABG.

Cel Pracy

Celem projektu jest retrospektywne przeprowadzenie analizy określającej wpływ przedoperacyjnego zastosowania małej dawki ASA (75mg/dobę) w zależności od czasu do zabiegu u pacjentów poddanych chirurgicznej rewaskularyzacji naczyń wieńcowych.

Materiał i metody

Retrospektywnie przeanalizowano dane 946 pacjentów poddanych izolowanej CABG pomiędzy Październikiem 2014 r. a Kwietniem 2018r. w Dolnośląskim Centrum Chorób Serca (DCChS) Medinet-Nowa Sól. Pacjenci, którzy otrzymali 75 mg ASA w czasie do 24 godzin przed zabiegiem stanowili grupę badawczą i porównano z grupą pacjentów, u których zaprzestano podawania ASA 24- do 48- godzin przed zabiegiem. Projekt pracy był zatwierdzony przez komisję etyczną DCChS Medinet oraz przez komisję bioetyczną Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu.

W pierwszym badaniu, 696 pacjentów zostało włączonych do badania wg kryteriów włączenia i zostali podzieleni na grupy w zależności od czasu otrzymania ostatniej dawki ASA przed CABG. Głównym ocenianym parametrem było wystąpienie AKI w jakimkolwiek stadium zgodnie z kryteriami KDIGO (Kidney Disease Improving Global Outcomes). Definicja AKI obejmowała: wzrost stężenia kreatyniny o $\geq$ 0.3mg/dl w ciągu 48 godzin lub wzrost stężenia kreatyniny o $\geq$ 1.5 razy wartości kreatyniny mierzonej w poprzedzających 7 dniach lub wydalanie moczu $\leq$ 0.5 ml/kg/h przez 6 godzin. Rutynowo wartość kreatyniny była mierzona przed operacją, 24, 48 i 72 godzin po operacji oraz przy wypisie. Użyto maksymalną wartość kreatyniny pomiędzy 24 a 48 godzin od operacji, aby ocenić wystąpienie AKI w ciągu 48 godzin. Rutynowo mierzono godzinową objętość wydalonego moczu w ciągu pierwszych 72 godzin po zabiegu. Poza tym, oceniano również współczynnik przesączania kłębuszkowego eGFR (estimated glomerular filtration rate) który był wyliczony za pomocą równania MDRD (Modification of Diet in Renal Disease).

W drugim badaniu, 652 pacjentów zostało włączonych wg kryteriów włączenia i zostali podzieleni na grupy w zależności od czasu otrzymania ostatniej dawki ASA przed CABG. Parametry oceny skuteczności obejmowały 30-dniową śmiertelność, wystąpienie niepożądanych incydentów sercowo-mózgowych (MACCE - Major adverse cardiac and cerebral events) oraz złożone zdarzenia śmiertelność + MACCE analizowane w ciągu 30 dni od zabiegu. MACCE było zdefiniowane jako wystąpienie zawału serca lub niepożądanego incydentu mózgowego (CAEs - cerebral adverse events). Zawał serca był zdefiniowany wg trzeciej uniwersalnej definicji zawału serca. CAE było zdefiniowane jako wystąpienie udaru mózgu lub przemijającego ataku niedokrwienia mózgu. Parametry oceny bezpieczeństwa obejmowały drenaż pooperacyjny mierzony 12 oraz 24 godzin od operacji, liczbę przetoczeń substancji krwiopochodnych oraz liczbę wystąpień reoperacji z powodu krwawienia pooperacyjnego.

W obydwu pracach, grupy były poddane analizie wieloczynnikowej, aby ocenić potencjalne czynniki ryzyka. Aby zredukować błędy statystyczne związane z obserwacyjnym charakterem projektu, zastosowano metodę propensity score matching aby porównać wyniki pomiędzy dwoma grupami.

Wyniki

W pierwszym badaniu, analiza wieloczynnikowa wykazała, że zastosowanie ASA w czasie do 24 godzin przed CABG istotnie zmniejszyło ryzyko wstąpienia AKI o 36 % (Iloraz szans: 0.64; 95% CI: 0.45-0.91; p=0.014). Wykazano też, że innymi istotnymi czynnikami zwiększającymi ryzyko wystąpienia AKI w okresie pooperacyjnym były: wiek, wskaźnik BMI, stosowanie leków inotropowych oraz transfuzja KKCz.

Analiza za pomocą metody propensity score matching potwierdziła poprzedni wynik - zastosowanie ASA w czasie do 24 godzin przed CABG istotnie zmniejszyło ryzyko

wstąpienia AKI w porównaniu do grupy, która otrzymała ASA 24 do 48 godzin przed CABG (25.1 % vs 36.8 %, p=0.004). Przed operacją stężenie kreatyniny oraz eGFR nie różnił się pomiędzy dwoma grupami. Przy wypisie tych pacjentów ze szpitala, zaobserwowano istotnie niższe stężenia kreatyniny oraz wyższy eGFR u pacjentów, którzy otrzymali ASA w czasie do 24 godzin przed CABG w porównaniu do grupy, która otrzymała ASA 24 do 48 godzin przed CABG. Ponadto, eGFR przy wypisie był istotnie wyższy w porównaniu do eGFR przy przyjęciu u pacjentów, którzy otrzymali ASA w czasie do 24 godzin przed CABG (średnia różnica: 6.13ml/min/1.73m^2;95%CI:2.06-10.19; p=0.003). Natomiast u pacjentów, którzy otrzymali ASA w czasie 24 do 48 godzin przed CABG nie zaobserwowano istotnego wzrostu eGFR (średnia różnica: 3.22ml/min/1.73m^2;95%CI: -0.27–6.71; p=0.07).

W drugiej pracy, analiza wieloczynnikowa wykazała, że zastosowanie ASA w czasie do 24 godzin przed CABG istotnie zmniejszyło 30-dniową śmiertelność o 75 % (iloraz szans: 0.25; 95% CI, 0.07 - 0.91; p=0.036). Wykazano również, że innymi czynnikami zwiększającymi ryzyko 30-dniowej śmiertelności były: przewlekła choroba nerek oraz przetaczanie KKCz. Ponadto, stosowanie ASA w czasie do 24 godzin przed CABG istotnie zmniejszyło 30-dniowe MACCE o 57 % (iloraz szans: 0.43; 95% CI, 0.22-0.85; p=0.016). Innymi istotnymi czynnikami zwiększającymi wystąpienia MACCE były: aktywne palenie papierosów, choroba trzech naczyń wieńcowych oraz transfuzja KKCz.

Przed zastosowaniem metody propensity score matching, analiza wieloczynnikowa wykazała, że zastosowanie ASA w czasie do 24 godzin przed CABG istotnie zmniejszyło 30-dniowe złożone zdarzenia śmiertelność + MACCE o 55 % (iloraz szans: 0.45; 95% CI, 0.24-0.85; p=0.014). Po zastosowaniu metody propensity score matching, zastosowanie ASA w czasie do 24 godzin przed CABG istotnie zmniejszyło 30-dniowe złożone zdarzenia śmiertelność + MACCE o 59 % (iloraz szans: 0.41; 95% CI, 0.19-0.88; p=0.02).

Analiza podgrupy pacjentów, u których wykonano CABG bez użycia krążenia pozaustrojowego wykazała, że zarówno przed jak i po zastosowaniu metody propensity score matching, zastosowanie ASA w czasie do 24 godzin przed CABG istotnie zmniejszyło 30-dniowe złożone zdarzenia śmiertelność + MACCE.

Przed propensity score matching, nie było żadnych istotnych statystycznie różnic między grupami pod względem drenażu pooperacyjnego, liczbą przetoczonych substancji krwiopochodnych oraz reoperacji z powodu krwawienia. Natomiast, po zastosowaniu metody propensity score matching, zaobserwowano tendencje do zwiększonego ryzyka wystąpień reoperacji z powodu krwawienia u pacjentów, u których zastosowano ASA w czasie do 24 godzin przed CABG (p=0.09).

Wnioski

Kontynuacja przedoperacyjnego ASA do czasu zabiegu, gdzie ostatnia dawka przed operacją jest podana w czasie do 24 godzin przed CABG jest związana ze zmniejszoną 30-dniową śmiertelnością pooperacyjną, jak też ze zmniejszonym ryzykiem wystąpień AKI oraz niepożądanych incydentów sercowo-mózgowych. Korzyści z zastosowania ASA w czasie do 24 godzin przed operacją, pod kątem zmniejszonego ryzyka wystąpień złożonych zdarzeń śmiertelność + niepożądane incydenty sercowo-mózgowe, mogą być szczególnie zauważalne u pacjentów zakwalifikowanych do chirurgicznej rewaskularyzacji serca bez użycia krążenia pozaustrojowego.

STRESZCZENIE W WERSJI ANGIELSKIEJ

Introduction

Acetylsalicylic acid (ASA) is one of therapeutic mainstays in patients suffering from coronary artery disease. The main advantage of ASA therapy was found to lay in primary and secondary prevention of cardiovascular events. It is a scientifically well-established fact that postoperative administration of ASA within first 48 hours following coronary artery bypass grafting (CABG) improves postoperative survival and reduces prevalence of cardiovascular ischemic events. When administered within 6 hours following CABG, it could positively affect such postoperative outcomes as saphenous vein graft patency. However, the use of preoperative ASA and the time interval required for preoperative discontinuation of ASA remains controversial. The 2017-European Association for Cardio-Thoracic Surgery Guidelines on perioperative medication in adult cardiac surgery states that continuation of ASA through the preoperative period in patients before CABG should be considered (Class-IIa). Whereas, the 2012-Update to the Society of Thoracic Surgeons Guideline on Use of Antiplatelet Drugs in Patients Having Cardiac and Noncardiac Operations states that ASA discontinuation is reasonable before elective CABG to decrease the risk of bleeding. Therefore, current perioperative management of preoperative ASA in patients prior CABG is variable. Till this day, continuation or the discontinuation time of preoperative ASA is related to the cardiac surgeon's preferences. Many surgeons continue ASA till the day of surgery; others discontinue several days prior CABG mainly because ASA could increase the risk of bleeding.

It is commonly believed that the thrombotic and ischemic events are increased in patients following CABG due to induced inflammatory response caused by extracorporeal circulation and its effect in promoting endothelial injury or due to hypercoagulable state and platelet hyperactivity developed after Off-pump CABG. On the other hand, acute kidney injury (AKI) is a common postoperative complication in patients following cardiac surgery. AKI incidence is estimated to reach 43% and it was shown that AKI following cardiac surgery negatively affects long-term survival, even in those with minor kidney injury. Several risk factors were reported to increase the incidence of AKI following cardiac surgery. Among those unmodifiable risk factors are such as age, hypertension, diabetes and peripheral vascular disease. Other such as the use of cardiopulmonary bypass (CPB), blood products transfusion, preoperative and intraoperative medications could also increase the risk of postoperative AKI.

Therefore, the antiplatelet and anti-inflammatory effects of ASA in the perioperative period might be responsible for the prevention and reduction of early thrombo-ischemic events and postoperative AKI following surgical revascularization as seen in the recent meta-analysis developed by our group. This meta-analysis emphasized the importance of preoperative, low-dose ASA which was found to be associated with the reduction in mortality rate, acute kidney injury as well as reduced incidence of perioperative myocardial infarction following CABG. Although it was found to benefit patients following surgical revascularization, preoperative ASA increased the risk of postoperative bleeding but without an increase in the need for chest re-exploration or red blood cell transfusions when low-dose ASA was maintained. Interestingly, in most of the studies examining the effect of preoperative ASA on patients submitted to CABG, the time of discontinuation of ASA varied between 1 to 6 days preoperatively. Due to discontinuation time variation between these studies, none of the available meta-analyses were able to examine the effect of the time interval between ASA withdrawal and CABG. The anti-inflammatory action of ASA is mediated by several

mechanisms, including interplay between platelets, endothelium and leukocytes. Due to irreversible inhibition of platelets' cyclooxygenase (COX) by acetylsalicylic acid, duration of its effects is solely determined by the target protein re-synthesis. In case of matured platelets, their full replacement over a few days is needed to recover COX activity, whereas, in case of endothelium, several hours are required to restore COX activity. However, Recent studies showed that platelet function gradually normalizes within 72 hours reaching full recovery within 96 hours after ASA withdrawal. Therefore, cessation of ASA few days prior to CABG eliminates the anti-inflammatory action of ASA and could lead to partial if not complete recovery of platelet function. That in turn might lead to an increased risk of thrombotic and ischemic events in the postoperative period. Therefore, continuation of ASA until the day of surgery could, in theory, improve postoperative outcomes and validate observation provided by Deng et al. who showed that continuation of ASA within 24 h of CABG is associated with the reduced mortality.

Aim of the study

We aimed to determine the impact of discontinuation of ASA on early postoperative outcomes according to time intervals in patients following CABG

Materials and methods

We aimed at collecting, reviewing and analyzing data of 946-patients who underwent primary, isolated, nonemergent CABG. Enrollment of eligible patients was performed within the period between October-2014 and April-2018 in the Department of Cardiac Surgery, Medinet Heart Centre Ltd, Nowa Sol-Poland. Patients who were administered with preoperative ASA (75 mg) 24-hours or less before CABG and those who were given ASA (75 mg) between 24-and 48-hours before CABG were all included in the analysis. The study was approved by the institutional review board at Medinet Heart Center and by the Bioethics

Committee of Wroclaw Medical University, Wroclaw, Poland. An individual patient consent to anonymous storing and analyzing the data was waived by the Ethics Committee.

In the first study, 696-met the inclusion criteria and were assigned to groups according to the time interval between their last ASA dose and the time of surgery. Primary outcome was defined as a development of a new onset of Acute Kidney Injury of any stage according to diagnostic criteria of the Kidney Disease Improving Global Outcomes guidelines and definitions (KDIGO). AKI was defined as one of the following: An increase in serum creatinine by $\geq$ 0.3mg/dl within 48-hours or an increase in serum creatinine to $\geq$ 1.5 times baseline within the previous 7-days or volume of urine output $\leq$ 0.5 ml/kg/h for 6-hours. Creatinine levels were routinely measured at baseline, before the operation, 24-hours, 48-hours, 72-hours after surgery and at discharge – postoperative day no - 7. We used the maximum level of creatinine between 24-and 48-hours to evaluate AKI within 48-hours. Urine volume was routinely monitored on hourly basis for the first 72-hours. Estimated glomerular filtration rate (eGFR) was calculated according to Modification of Diet in Renal Disease formula (MDRD).

In the second study, 652 patients met the inclusion criteria and were assigned to groups according to the interval between their last ASA dose and the time of surgery. Efficacy endpoints included 30-day all-cause mortality, early incidence of major adverse cardiac and cerebral events (MACCE) and composite rate of 30-day mortality and MACCE. MACCE was defined as the occurrence of MI and cerebral adverse events (CAEs). MI was defined according to the third international definition of myocardial infarction. CAEs were defined as development of a new permanent or transient (lasting up to 72 hours) neurologic deficit as confirmed by stroke team member assessment of the patient and computed tomography, magnetic resonance imaging or at autopsy examination. Safety endpoints included

postoperative chest tube drainage at t=12 and 24 hours postoperatively, postoperative transfusion rate of blood products and incidence of postoperative re-explorations for bleeding. In both studies, Multivariable analysis was performed to identify possible risk factors. To reduce any selection bias due to lack of randomization, propensity score matching (PSM) was used to match patients in between both groups.

Results

In the first study, Multivariable analysis in the entire cohort showed that administration of ASA within 24-hours before CABG is independently associated with the reduction of AKI incidence by 36 % (OR: 0.64; 95% CI: 0.45-0.91; p=0.014). Other significant predictors for increased incidence of AKI were age, BMI, the use of inotropic support and pRBC transfusions. Propensity score matching maintained this finding and showed that patients receiving ASA within 24-hours prior CABG had lower incidence of AKI in comparison to patients who discontinued ASA between 24- and 48-hours before CABG (25.1 % vs 36.8 %, p=0.004)(OR: 0.56; 95% CI: 0.38-0.83),respectively. On the other hand, at baseline, serum creatinine level and eGFR did not differ between the groups. However, there were significantly lower serum creatinine levels and higher eGFRs in patients receiving ASA within 24-hours prior CABG postoperatively. Significantly higher glomerular filtration rate at discharge was seen not only between the groups but also in comparison to baseline in patients receiving ASA within 24-hours prior CABG (mean difference MD: 6.13ml/min/1.73m^2; 95% CI: 2.06-10.19; p=0.003). Similar effect was absent in patients who discontinued ASA between 24- and 48-hours before CABG (MD: 3.22ml/min/1.73m^2; 95% CI: -0.27–6.71; p=0.07).

In the second study, multivariable analysis showed that ASA administration within 24 hours of CABG was independently associated with the reduction of 30-day mortality by 75% (OR: 0.25; 95% CI: 0.07 -0.91; p=0.036). Other significant predictors of 30-day mortality was renal

insufficiency as well as packed red blood cell transfusions (pRBC). Also, multivariable analysis showed that preoperative ASA within 24 hours before CABG significantly reduced the incidence of MACCE by 57 % (OR: 0.43; 95% CI: 0.22-0.85; p=0.016). Active smoking, previous CAEs, ≥3-vessel disease and pRBC transfusions were all found to be significant predictors for an increased incidence of MACCE.

Before propensity score matching, multivariable analyses showed that ASA within 24 hours before CABG was independently associated with the reduction of composite rates of 30-day mortality/MACCE by 55 % (OR: 0.45; 95% CI: 0.24-0.85; p=0.014). After matching, ASA within 24 hours before CABG still reduced independently composite rates of 30-day mortality/MACCE by 59 % (OR: 0.41; 95% CI: 0.19-0.88; p=0.02).

Subgroup analysis in patients following off-pump CABG (OPCAB) was performed with propensity score matching. Multivariate analysis before matching showed that ASA within 24 hours before OPCAB was independently associated with reduced composite rates of 30-day mortality/MACCE by 63 % (OR: 0.37; 95% CI: 0.17-0.80; p=0.012). After matching, there was no difference between both groups with regards to preoperative risk factors. After matching, ASA within 24 hours still reduced independently composite rates of 30-day mortality/MACCE by 80 % in patients following OPCAB (OR:0.20; 95% CI: 0.07-0.55; p=0.002)

Before propensity score matching, there were no significant differences between both groups in terms of safety outcomes such as postoperative bleeding, blood transfusions and reoperation for bleeding. However, after propensity score matching, a trend towards increased incidence of reoperation for bleeding was observed in patients who took ASA within 24 hours before CABG (p=0.09).

Conclusion

Continuation of ASA until the day of surgery, with the last ASA dose administration within 24 hours prior to CABG seems safe and is independently associated with reduced 30-day mortality rate as well as MACCE and AKI after CABG. The evidence also suggests that ASA within 24 hours or less was specifically associated with reduced composite rates of early mortality and MACCE in patients following OPCAB.

Rozdział II

Publikacja A.1

The Journal of Thoracic and Cardiovascular Surgery

ASSOCIATION BETWEEN PREOPERATIVE ASPIRIN AND ACUTE KIDNEY INJURY FOLLOWING CORONARY ARTERY BYPASS GRAFTING.

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Sleiman Sebastian Aboul-Hassan, Jakub Marczak, Tomasz Stankowski, Maciej Peksa, Marcin Nawotka, Ryszard Stanislawski, Romuald Cichon. Association Between Preoperative Aspirin And Acute Kidney Injury Following Coronary Artery Bypass Grafting. J Thorac Cardiovasc Surg. 2019. 2019 Sep 25. doi: 10.1016/j.jtcvs.2019.08.119. [Epub ahead of print]

(IF = 5.261, Pkt. MNiSW/KBN: 140.000)

Association between preoperative aspirin and acute kidney injury following coronary artery bypass grafting

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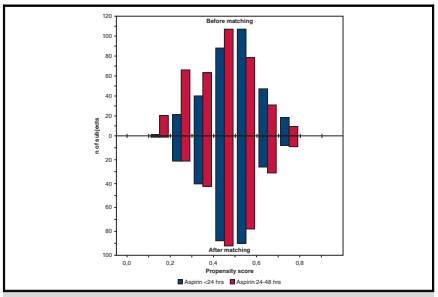
ABSTRACT

Objective: To test the hypothesis that preoperative aspirin administered within 24 hours before coronary artery bypass grafting (CABG) could reduce the incidence of postoperative acute kidney injury (AKI) following CABG.

Methods: In this retrospective study, 696 patients were assigned to groups according to the time interval between their last aspirin dose administration and the time of surgery. A total of 322 patients received aspirin ≤24 hours before CABG, and 374 patients received aspirin between 24 and 48 hours before CABG. The primary outcome was postoperative AKI of any stage as defined by the Kidney Disease Improving Global Outcomes criteria. Propensity score matching selected 274 pairs for the final comparison.

Results: Multivariable analysis showed that administration of aspirin within 24 hours of CABG was independently associated with reduction of AKI incidence by 36% (odds ratio, 0.64; 95% confidence interval, 0.45-0.91; $P = .014$). It was also noted that patients receiving their last aspirin dose ≤24 hours before CABG had a significantly higher glomerular filtration rate at discharge compared with patients who received aspirin between 24 and 48 hours before CABG. Propensity score matching analysis showed that patients receiving aspirin within 24 hours before CABG had a lower incidence of AKI compared with patients who discontinued aspirin between 24 and 48 hours before CABG (25.1% vs 36.8%; $P = .004$).

Conclusions: Continuation of aspirin until the day of surgery, with the last aspirin dose administered ≤24 hours before CABG, is associated with a significant reduction of postoperative AKI. (J Thorac Cardiovasc Surg 2019;■:1-9)



A propensity score analysis delivered a well-matched cohort for studying the effect of preoperative aspirin on acute kidney injury.

Central Message

Continuation of preoperative aspirin with the last dose administered ≤24 hours before coronary artery bypass grafting correlates with a significantly reduced incidence of postoperative acute kidney injury.

Perspective

This study was designed to evaluate the impact of preoperative aspirin on postoperative renal function status following coronary artery bypass grafting (CABG). With the use of propensity score matching and multivariable analysis, the study provides contemporary clinical information regarding the use of preoperative aspirin with its timing strategy and its effect on postoperative renal function following CABG.

See Commentary on page XXX.

PM

Acute kidney injury (AKI) is a common postoperative complication in patients following cardiac surgery, with an estimated incidence as high as 43%. AKI following cardiac surgery is known to negatively affect long-term survival, even in those with minor kidney injury.[1,2] Several risk factors have been reported to increase the incidence of AKI following cardiac surgery. Among those unmodifiable risk factors are age, hypertension, diabetes, and peripheral vascular disease.[3] Others, such as the use of cardiopulmonary bypass (CPB), blood product transfusion, and preoperative and intraoperative medications, also can

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Abbreviations and Acronyms

AKI = acute kidney injury
CABG = coronary artery bypass grafting
CI = confidence interval
COX = cyclooxygenase
CPB = cardiopulmonary bypass
eGFR = estimated glomerular filtration rate
MD = mean difference
pRBC = packed red blood cell
PS = propensity score
SMD = standardized mean difference

increase the risk of postoperative AKI.[4] Although the etiology of AKI is multifactorial, several pathophysiological processes may have important effects on the development of postoperative AKI. These include endothelial dysfunction, microcirculatory dysfunction, formation of microvascular thrombosis, tubular injury, and intrarenal inflammation, altering renal perfusion and consequently leading to development of AKI.[5]

Because of its antiplatelet and anti-inflammatory effect, aspirin is considered a cornerstone therapy in patients suffering from coronary artery disease. In patients undergoing coronary artery bypass grafting (CABG), postoperative administration of aspirin within 48 hours is associated with reduced perioperative mortality and ischemic events, as well as with a decreased prevalence of renal failure.[6] Despite its benefit in patients following CABG, continuation or administration before CABG remains a matter of debate.[7] A recent meta-analysis showed that preoperative aspirin reduced the incidence of AKI by 32% in all cardiac surgery patients, where 72% of the included patients underwent CABG with or without concomitant valve surgery.[8] Therefore, the association between preoperative administration of aspirin and AKI following isolated CABG has not been fully evaluated. The antiplatelet and anti-inflammatory effects of preoperative aspirin could reduce inflammation as well as thrombotic events in patients following CABG. The systemic inflammatory response following CABG is believed to be increased due to endothelial injury and inflammatory response secondary to the use of cardiopulmonary bypass.[9-12] Therefore, preoperative aspirin may potentially reduce the risk of microvascular thrombi formation and ameliorate inflammatory processes following CABG, thereby reducing the risk of postoperative AKI.

The anti-inflammatory action of aspirin is mediated by several mechanisms, including interplay among platelets, endothelium, and leukocytes. Because of the irreversible inhibition of platelets' cyclooxygenase (COX) by acetylsalicylic acid, the duration of its effects is determined solely by the target protein resynthesis. In case of matured platelets, their full replacement over a few days is needed to recover COX activity, whereas in endothelium, several hours are required to restore COX activity.[13] Our present study was been designed to test the hypothesis that preoperative aspirin administered within 24 hours before CABG could reduce the incidence of postoperative AKI following CABG.

METHODS

Study Design

In this retrospective cohort study designed in accordance with the STROBE guidelines,[14] we collected, reviewed, and analyzed data of 946 patients who underwent primary, isolated, nonemergent CABG. Enrollment of eligible patients was performed between October 2014 and April 2018 at the Department of Cardiac Surgery, Medinet Heart Centre, Nowa Sol, Poland. Patients who were administered preoperative aspirin (75 mg) ≤24 hours before CABG and those who were given aspirin (75 mg) 24 to 48 hours before CABG were included in the analysis. Exclusion criteria were patients with a missing or unclear preoperative medication history (n = 40), patients with documented intolerance to aspirin or who had not been taking aspirin for >7 days before the surgery (n = 16), patients who had not been taking aspirin for >48 hours before CABG for <7 days (n = 23), patients with end-stage renal failure requiring dialysis (n = 5), patients requiring emergent CABG (n = 5), patients already enrolled in an ongoing randomized controlled trial testing antiplatelet therapy following CABG (n = 31), patients who underwent minimally invasive CABG (n = 95), and patients who took >75 mg of aspirin before CABG (n = 35). Of the 946 patients, 696 met the inclusion criteria and were assigned to 1 of 2 groups according to the interval between their last aspirin dose and the time of surgery: patients who had been given aspirin ≤24 hours before CABG (n = 322) and those who had been given the last dose of aspirin 24 to 48 hours before CABG (n = 374). Figure 1 represents STROBE flow diagram. The study was approved by the Institutional Review Board of Medinet Heart Center and the Bioethics Committee of Wroclaw Medical University, Wroclaw, Poland. An individual patient consent to anonymous storing and analyzing the data was waived by the Ethics Committee.

Study Data

Patient demographic data, clinical characteristics, medications, and postoperative outcomes were retrieved from the cardiac surgical database at Medinet Heart Center. The dosage and timing of preoperative aspirin were obtained from medication charts. Data on preoperative dose and time of the last aspirin administration in patients admitted to the hospital the day before surgery were obtained from preoperative medication questionnaires. As for patients transferred from other departments, data on the dosage and timing of preoperative aspirin were obtained from discharge letters. The circuit prime for CPB in patients undergoing on-pump CABG was standardized and consisted of Ringer's solution, 200 mL of mannitol (200 mg/mL), and heparin. Postoperatively, all patients received aspirin starting at 12 to 24 hours after CABG and continuing daily thereafter. Diuretics were used in the early postoperative period in all patients and were continued until discharge or as required. All of the patients in the postoperative period received statin therapy, which was continued indefinitely.

Study Endpoints

Primary outcome was defined as a development of new-onset AKI of any stage according to diagnostic criteria of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines and definitions.[15] AKI was defined as 1 of the following: an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or an increase in serum creatinine to ≥1.5 times baseline within

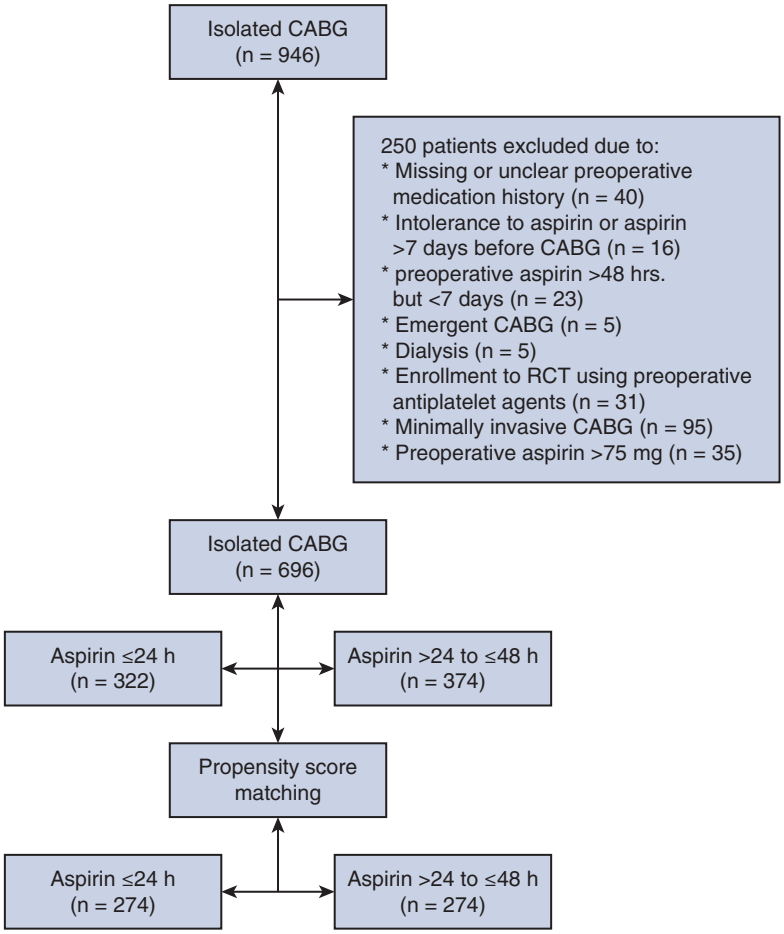

FIGURE 1. STROBE flow diagram detailing selection of patients within each group. The diagram presents included and excluded patients, as well as the number of patients before and after propensity score matching. *CABG*, Coronary artery bypass grafting; *RCT*, randomized controlled trial.

the previous 7 days or volume of urine output ≤0.5 mL/kg/hours for 6 hours. Creatinine levels were routinely measured at baseline, before the operation; at 24 hours, 48 hours, and 72 hours after surgery; and at discharge, on postoperative day 7. We used the maximum creatinine level between 24 and 48 hours to evaluate AKI within 48 hours. Urine volume was routinely monitored on hourly basis for the first 72 hours. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula.[16]

Statistical Analysis

All statistical analyses were performed using Statistica version 13 (Tibco, Palo Alto, Calif). Continuous variables are expressed as mean ± SD; categorical variables, as number and percentage. For continuous data distribution, the Student *t* test was used for between-group comparisons, and categorical variables were compared using the Pearson χ^2 test.

To identify independent predictors of AKI, we built a multivariable logistic regression model for the whole cohort by using all preoperative variables presented in Table 1 in addition to operative and postoperative outcomes, such as type of surgery (on-pump or off-pump CABG), duration of the surgery, number of grafts performed, inotropic support, total arterial revascularization, and packed red blood cell (pRBC) transfusion. Multivariable logistic regression analysis was performed using stepwise backward regression including only factors identified during univariate analysis with a *P* value ≤.1.

To reduce the risk of selection bias, propensity score (PS) matching was used to match patients who took aspirin (75 mg) within 24 hours before CABG with patients who took aspirin (75 mg) between 24 and 48 hours before surgery. PSs were generated from a multivariable logistic regression model based on 15 preoperative variables: age, sex, peripheral vascular disease, body mass index, left ventricular ejection fraction, diabetes, number of diseased vessels, preoperative eGFR, renal impairment, preoperative medication ≤24 hours (ie, beta-blockers, statins, renin-angiotensin-aldosterone inhibitors, diuretics, calcium channel blockers), and preoperative hematocrit. Patients were then matched in 1:1 fashion using a caliper matching method without replacement with a caliper width of 0.2 SD of the logit of the PS.[17,18] The balance of the covariates was tested using the standardized mean difference (SMD). After matching, the 2 groups were comparable for preoperative confounders ($-0.1 < \text{SMD} < 0.1$) (Table 1). A mirrored histogram showed adequate PS overlapping (Figure 2). Matched data were analyzed using procedures for matched analyses. Wilcoxon's matched pairs test was used for continuous data, and McNemar's test was used for binary outcomes. Statistical significance was defined by a *P* value <.05.

RESULTS

Between October 2014 and April 2018, 696 patients met the inclusion criteria and were subsequently divided into 2 groups: those who were given aspirin (75 mg) up to 24 hours

TABLE 1. Baseline characteristics of patients undergoing CABG

Characteristic	Before matching			After matching			
	Aspirin ≤24 h (n = 322)	Aspirin >24-≤48 h (n = 374)	*P* value	Aspirin ≤24 h (n = 274)	Aspirin >24-≤48 h (n = 274)	*P* value	SMD
Age, y, mean ± SD	64.75 ± 8.14	65.38 ± 7.70	.31	65.04 ± 7.89	65.1 ± 7.84	.88	−0.01
Female sex, n (%)	69 (21.4)	112 (29.9)	.01	65 (23.7)	65 (23.7)	1	0.000
PVD, n (%)	72 (22.3)	78 (20.8)	.63	58 (21.1)	60 (21.8)	.83	−0.023
BMI, kg/m^2, mean ± SD	28.41 ± 4.62	29.06 ± 4.63	.08	28.53 ± 4.66	28.7 ± 4.8	.61	−0.04
LVEF, %, mean ± SD	48.69 ± 10.2	50.09 ± 9.96	.23	49.75 ± 9.78	49.5 ± 9.8	.81	0.02
Moderate LVEF (31%-50%), n (%)	163 (50.6)	194 (51.8)	.74	134 (48.9)	147 (53.6)	.26	
Poor LVEF (≤30%), n (%)	36 (11.1)	25 (6.6)	.03	30 (10.9)	22 (8.0)	.24	
History of CAEs, n (%)	39 (12.1)	48 (12.8)	.77	35 (12.7)	34 (12.4)	.89	
Diabetes, n (%)	111 (34.4)	142 (37.9)	.33	95 (34.6)	93 (33.9)	.85	0.017
Recent MI (<90 d), n (%)	133 (41.3)	146 (39.0)	.54	107 (39.0)	111 (40.5)	.72	
Previous MI (>90 d), n (%)	56 (17.3)	53 (14.1)	.24	47 (17.1)	45 (16.4)	.81	
NYHA III-IV, n (%)	39 (12.1)	34 (9.0)	.19	31 (11.3)	23 (8.3)	.25	
Number of diseased vessels, mean ± SD	2.99 ± 0.99	2.99 ± 0.95	1	2.97 ± 0.97	2.98 ± 1	.9	−0.01
One-vessel disease, n (%)	20 (6.2)	25 (6.6)	.8	19 (6.9)	16 (5.8)	.6	
Two-vessel disease, n (%)	73 (22.6)	71 (18.9)	.23	61 (22.2)	52 (18.9)	.34	
≥Three-vessel disease, n (%)	229 (71.1)	278 (74.3)	.19	194 (70.8)	206 (75.1)	.24	
Urgent surgery, n (%)	193 (59.9)	216 (57.7)	.55	160 (58.3)	159 (58.0)	.93	
Previous PCI, n (%)	89 (27.6)	95 (25.4)	.50	77 (28.1)	75 (27.3)	.84	
Active smoker, n (%)	126 (39.1)	118 (31.5)	.03	105 (38.3)	93 (33.9)	.28	
Hypertension, n (%)	300 (93.1)	343 (91.7)	.47	254 (92.7)	250 (91.2)	.53	
Hyperlipidemia, n (%)	210 (65.2)	236 (63.1)	.56	181 (66.0)	176 (64.2)	.65	
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	84.35 ± 22.96	82.13 ± 22.63	.20	82.89 ± 21.94	83.2 ± 22.9	.83	−0.02
Renal impairment, n (%)	177 (54.9)	223 (59.6)	.21	157 (57.2)	158 (57.6)	.93	−0.008
Moderate impairment	161 (50)	199 (53.2)	.39	142 (51.8)	142 (51.8)	1	
Severe impairment	16 (4.9)	24 (6.4)	.41	15 (5.4)	16 (5.8)	.85	
Preoperative medications ≤24 h, n (%)							
Beta-blockers	225 (69.8)	207 (55.3)	.0001	180 (65.6)	180 (65.6)	1	0.000
RAASI	96 (29.8)	106 (28.3)	.66	80 (29.1)	84 (30.6)	.70	−0.038
Statins	258 (80.1)	241 (64.4)	.0000	212 (77.3)	214 (78.1)	.83	−0.023
Diuretics	53 (16.4)	30 (8.0)	.0008	29 (10.5)	29 (10.5)	1	0.000
CCB	16 (4.9)	34 (9.0)	.0385	14 (5.1)	15 (5.4)	.84	−0.04
Clopidogrel ≤7 d	41 (12.7)	52 (13.9)	.65	34 (12.4)	38 (13.8)	.61	
Preoperative Hgb level, g/dL, mean ± SD	14.24 ± 1.37	14.18 ± 1.48	.58	14.26 ± 1.36	14.28 ± 1.53	.87	
Preoperative hematocrit, %, mean ± SD	41.84 ± 3.99	41.58 ± 4.45	.42	41.86 ± 3.99	41.84 ± 4.34	.95	0.000

Renal impairment defined as eGFR <85 mL/min/1.73 m^2; moderate renal impairment, as eGFR >50 and <85 mL/min/1.73 m^2; severe impairment, as eGFR<50 mL/min/1.73 m^2. *SMD*, Standardized mean difference; *PVD*, peripheral vascular disease; *BMI*, body mass index; *CAE*, cerebral adverse event; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *RAASI*, renin-angiotensin-aldosterone inhibitor; *CCB*, calcium channel blocker; *Hgb*, hemoglobin.

before CABG (n = 322) and those who discontinued aspirin between 24 and 48 hours before CABG (n = 374). Baseline and operative characteristics of the 2 groups are presented in Tables 1 and 2, respectively. The 2 groups did not differ in terms of age, left ventricular ejection fraction, diabetes, peripheral vascular disease, moderate or severe renal

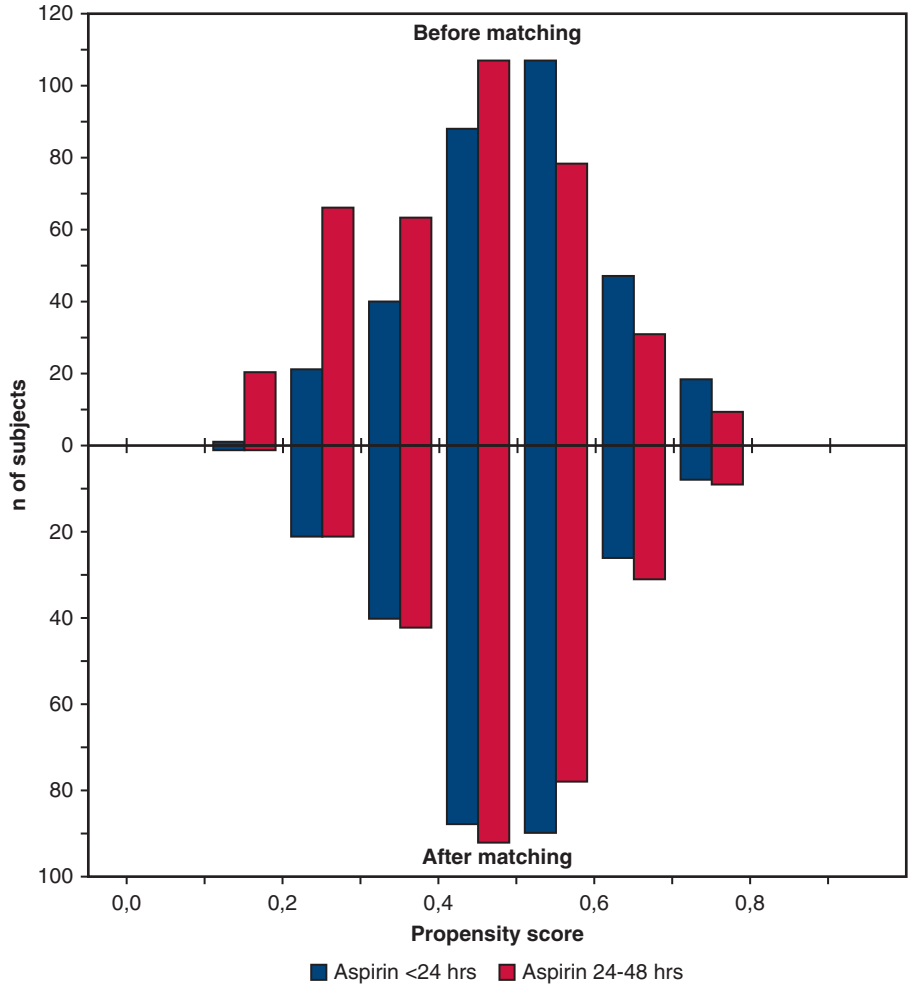

FIGURE 2. Mirrored histogram showing the propensity score distribution before (*top*) and after matching (*bottom*) in both groups. Before matching, preoperative characteristics varied between the groups. After matching, there were no significant differences between the matched groups. The blue bars represent patients receiving preoperative aspirin ≤24 hours before coronary artery bypass grafting (CABG), whereas the orange bars represent those patients receiving aspirin between 24 and 48 hours before CABG.

impairment, heart failure symptoms, and history of recent or previous myocardial infarction. However, female patients were more prevalent in the group in which aspirin was discontinued 24 to 48 hours before CABG, whereas active smokers were more prevalent in the aspirin ≤24 hours group. Concurrent preoperative medications

TABLE 2. Operative characteristics

	Before matching			After matching		
Characteristic	Aspirin ≤24 h (n = 322)	Aspirin>24-≤48 h (n = 374)	*P* value	Aspirin ≤24 h (n = 274)	Aspirin >24-≤48 h (n = 274)	*P* value
Type of surgery, n (%)						
OPCAB	252 (78.2)	300 (80.2)	.52	215 (78.4)	219 (79.9)	.67
ONCAB	70 (21.8)	74 (19.8)	.52	59 (21.5)	55 (20.0)	.67
Duration, min, mean ± SD	169 ± 52	167 ± 49	.48	170 ± 51	166 ± 47	.33
Number of grafts, mean ± SD	2.47 ± 0.75	2.46 ± 0.74	.86	2.51 ± 0.72	2.44 ± 0.74	.27
Total arterial revascularization, n (%)	75 (23.2)	86 (22.9)	.92	64 (23.3)	60 (21.8)	.68

OPCAB, Off-pump coronary artery bypass grafting; *ONCAB*, on-pump coronary artery bypass grafting.

TABLE 3. Changes in serum creatinine level and eGFR before and after CABG

Parameter	Aspirin ≤24 h	Aspirin >24-≤48 h	MD (95% CI)	*P* value
Creatinine level, mg/dL, mean ± SD				
Baseline	0.99 ± 0.63	0.97 ± 0.26	0.02 (−0.05 to 0.09)	.57
24-48 h	1.14 ± 0.36	1.23 ± 0.51	−0.09 (−0.15 to −0.02)	.008
72 h	1.14 ± 0.41	1.22 ± 0.53	−0.08 (−0.14 to −0.01)	.028
At discharge	0.92 ± 0.27	0.97 ± 0.38	−0.05 (−0.1 to −0.00)	.049
eGFR, mL/min/1.73 m^2, mean ± SD				
Baseline	84.35 ± 22.96	82.13 ± 22.63	2.22 (−1.17 to 5.61)	.2
24-48 h	71.92 ± 25.32	67.37 ± 24.69	4.55 (0.82 to 8.27)	.016
72 h	74.82 ± 25.78	70.11 ± 25.71	4.71 (0.87 to 8.54)	.016
At discharge	90.48 ± 29.34	85.35 ± 26.00	5.13 (0.98 to 9.27)	.014

eGFR, Estimated glomerular filtration rate; *CABG*, coronary artery bypass grafting; *MD*, mean difference; *CI*, confidence interval.

administered to patients up to 24 hours preoperatively, such as beta-blockers, statins, or diuretics were more likely to be used in the aspirin ≤24 hours group. Alternatively, calcium channel blockers were more likely to be received by patients who discontinued aspirin 24 to 48 hours before CABG. There were no significant between-group differences in terms of operative characteristics, such as type of surgery (on-pump or off-pump), number of grafts performed, duration of surgery, and total arterial revascularization.

Multivariable analysis in the entire cohort showed that administration of aspirin within 24 hours before CABG was independently associated with a 36% lower incidence of AKI (odds ratio, 0.64; 95% confidence interval [CI], 0.45-0.91; $P = .014$). Other significant predictors for increased incidence of AKI were age, body mass index, the use of inotropic support, and pRBC transfusions.

At baseline, serum creatinine level and eGFR did not differ between the 2 groups; however, postoperatively, serum creatinine levels were significantly lower and eGFR was significantly higher in patients receiving aspirin within 24 hours before CABG (Table 3). The eGFR at discharge was significantly higher compared to baseline that group (mean difference [MD], 6.13 mL/min/1.73 m^2; 95% CI, 2.06-10.19; $P = .003$). A similar effect was absent in patients who discontinued aspirin between 24 and 48 hours before CABG (MD, 3.22 mL/min/1.73 m^2; 95% CI, −0.27 to 6.71; $P = .07$).

To reduce selection bias inherent to observational studies, PS analysis was used to match patients who were administered aspirin (75 mg) ≤24 hours preoperatively with patients who received aspirin (75 mg) between 24 and 48 hours preoperatively. PS matching selected 274 matched pairs for final comparison. The 2 matched groups were balanced ($-0.1 < SMD < 0.1$) (Table 1). A mirrored histogram showed adequate PS overlap (Figure 2). After matching, patients receiving aspirin within 24 hours before CABG had a lower incidence of AKI compared with patients who discontinued aspirin 24 to 48 hours before CABG (25.1% vs 36.8%; $P = .004$; odds ratio, 0.56; 95% CI, 0.38-0.83) (Table 4).

Before matching, patients who discontinued aspirin between 24 and 48 hours before CABG were significantly more prone to receiving postoperative renal replacement therapy compared with those who received aspirin within 24 hours before CABG (0.62% vs 3.4%; $P = .04$). However, after matching, there were no significant differences between the 2 groups in terms of renal replacement therapy (0.3% vs 1.8%; $P = .22$) (Table 4). In terms of safety outcomes, there were no significant differences between the 2 groups both before and after matching in terms of pRBC transfusions, reoperation for bleeding, and postoperative chest drainage (Table 4).

DISCUSSION

In this single-center study, we provide evidence in favor for continuation of aspirin until the time of coronary surgery. Our analysis shows that preoperative aspirin is associated with a significant reduction of postoperative acute kidney injury following CABG when given within 24 hours. Immediate aspirin pretreatment ≤24 hours before CABG was also found to be associated with higher eGFR in the postoperative period compared with baseline.

The mechanism of AKI following CABG is multifactorial. Several processes, including endothelial dysfunction, microcirculatory dysfunction, formation of microvascular thrombi, tubular injury, and intrarenal inflammation, can alter renal perfusion and lead to the development of AKI.[5] Activation of systemic inflammatory processes persisting for several days following CABG could inevitably cause alterations in microvascular function, which in turn may lead to hypoperfusion and ischemia of the kidney even in the absence of arterial hypotension.[5,19]

Endothelial function not only serves as a barrier within the renal microcirculation, but also facilitates and optimizes such processes as humoral homeostasis and maintenance and regulation of glomerular filtration.[5] Systemic inflammation leads to endothelial dysfunction and subsequent

TABLE 4. Postoperative outcomes following CABG

Outcome	Before matching			After matching		
	Aspirin ≤24 h (n = 322)	Aspirin>24-≤48 h (n = 374)	*P* value*	Aspirin ≤24 h (n = 274)	Aspirin >24-≤48 h (n = 274)	*P* value†
Acute kidney injury, n (%)	82 (25.4)	134 (35.8)	.03	69 (25.1)	101 (36.8)	.004
Renal replacement therapy, n (%)	2 (0.62)	11 (3.4)	.04	1 (0.3)	5 (1.8)	.22
Inotropic support, n (%)	70 (21.7)	98 (26.2)	.17	58 (21.1)	73 (26.6)	.16
Reoperation for bleeding, n (%)	17 (5.2)	15 (4.0)	.42	17 (6.2)	12 (4.3)	.44
Chest drainage at 24 h, mL, mean ± SD	662 ± 339	671 ± 363	.72	663 ± 342	698 ± 383	.54
Packed red blood cell transfusion, n (%)	148 (45.9)	174 (46.5)	.88	131 (47.8)	127 (46.3)	.79
0	174 (54.0)	200 (53.4)	.88	143 (52.1)	147 (53.6)	.79
1	12 (3.72)	16 (4.2)	.71	11 (4.0)	13 (4.7)	.83
2	68 (21.1)	81 (21.6)	.86	58 (21.1)	58 (21.1)	.91
3	13 (4.0)	11 (2.9)	.43	11 (4.0)	7 (2.5)	.47
≥4	55 (17.0)	66 (17.6)	.84	51 (18.6)	49 (17.8)	.91
Duration of hospital stay, d, mean ± SD	7.01 ± 2.81	7.33 ± 3.64	.20	7.05 ± 2.96	7.34 ± 3.49	.19

CABG, Coronary artery bypass grafting. *χ^2 test or *t* test. †McNemar test or Wilcoxon matched-pairs test.

microcirculatory failure. In addition, endothelial dysfunction enhances leukocyte–endothelium interaction, leading to the migration of leukocytes toward the renal interstitium, inducing tubular cell injury.[20-22] Activation of coagulation due to endothelial dysfunction leads to formation of microvascular thrombi.[23] Therefore, systematic inflammation, as well as the recruitment of leukocytes, are considered the main mediators of endothelial and tubular dysfunction leading to postoperative AKI.[24] Aspirin, even at low doses, has been shown to have anti-inflammatory action by triggering 15-epi-lipoxin A4 from the endothelial cells, preventing leukocyte accumulation and activation in the injured tissue in a nitric oxide–dependent manner.[25] Aspirin-triggered lipoxins can reduce endothelium-derived production of reactive oxygen species and have been shown to reduce leukocyte adhesion to the endothelial cells, thereby reducing inflammation in the microvasculature.[26-28] On the other hand, lipoxins released by leukocyte-platelet aggregates regulate the activation and adhesion of the leukocytes, reducing vascular wall damage.[29] Therefore, through these anti-inflammatory mechanisms, aspirin could play an important role in improving renal function in the postoperative period.

However, due to its irreversible inhibition of cyclooxygenase (COX), the duration of its effects is determined by the target protein resynthesis. In case of mature platelets, new ones are needed to recover COX, whereas in other tissues, such as endothelium, only several hours are needed to restore COX activity.[13] After withholding the chronic use of aspirin, full recovery of platelet function is observed even after 96 hours.[30] Partial recovery of the platelet function might be obtained after stopping aspirin between 24 and 48 hours, which in turn may enhance the formation of microvascular thrombi in the kidneys due to the greater magnitude of systemic inflammation.

Despite clear recommendations for the use of aspirin after CABG, guideline recommendations as to its continuation or administration before surgery are inconsistent. The 2017 European Association for Cardio-Thoracic Surgery Guidelines on perioperative medication in adult cardiac surgery states that continuation of aspirin through the preoperative period before CABG should be considered (class IIa).[31] In contrast, the 2012 update to the Society of Thoracic Surgeons Guideline on Use of Antiplatelet Drugs in Patients Having Cardiac and Noncardiac Operations states that aspirin discontinuation is reasonable before elective CABG to decrease the risk of bleeding.[32] Therefore, current perioperative management of preoperative aspirin in patients before CABG is variable. Continuation or discontinuation of preoperative aspirin is based on the cardiac surgeon's preference. Many surgeons continue aspirin to the day of surgery, whereas others discontinue it several days before CABG, mainly because aspirin can increase the risk of bleeding. This was shown in a recent meta-analysis, where in most of the studies, the discontinuation time of aspirin in patients receiving aspirin preoperatively ranged from 1 day to 6 days.[8]

In this study, we aimed to test the hypothesis that the anti-inflammatory effect of aspirin might be beneficial to the preservation of renal function in the setting of CABG without any additional risk for postoperative bleeding. Our analysis of the data found that continuation of aspirin until the day of surgery was associated with a significant reduction of postoperative AKI following CABG. Several

studies have analyzed risk factors for AKI following cardiac surgery. These risk factors are divided into preoperative, operative, and postoperative, and most of them were taken into consideration in this study.[4] One of the main operative risk factors for AKI following CABG is the use of CPB. There is an evidence in the literature showing an association between the use of CPB and an increased risk of postoperative AKI.[33,34] In our study, AKI in patients following on-pump and off-pump CABG did not differ significantly (33.3% vs 30.4%; $P = .50$). This possibly could be explained by the high proportion of patients undergoing off-pump CABG, which might have had an impact on the results, given the low relative weight of patients who underwent on-pump CABG.

AKI following cardiac surgery could affect long-term-mortality,[1] even in patients with mild kidney injury following the operation.[2] Therefore, we believe that aspirin $\leq$24 hours before CABG could reduce the effect of postoperative AKI on long-term-mortality.

This study has several limitations. First, it is a single-center, retrospective study, and patients were not randomized to continue preoperative aspirin or not. To limit the inherent risks of potential selection bias, a PS matching procedure was implemented. Second, some risk factors, such as hypoalbuminemia, were not analyzed. Third, the impact of preoperative aspirin on inflammatory mediators that could induce AKI following CABG were not analyzed in this study. Finally, the impact of decreased urine output during CPB and its possible effect on AKI was not analyzed in this study.

In conclusion, continuation of aspirin until the day of surgery, with the last aspirin dose given $\leq$24 hours before CABG, is associated with a significant reduction of postoperative AKI.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: preoperative aspirin, CABG, AKI, renal failure

PM

000 Association between preoperative aspirin and acute kidney injury following coronary artery bypass grafting

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Continuation of preoperative aspirin with the last dose administered $\leq$24 hours before coronary artery bypass grafting correlates with a significantly reduced incidence of postoperative acute kidney injury.

PM

Publikacja A.2

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TIMING STRATEGY OF PREOPERATIVE ASPIRIN AND ITS IMPACT ON EARLY OUTCOMES IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING: A PROPENSITY SCORE MATCHING ANALYSIS.

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Sleiman Sebastian Aboul-Hassan, Tomasz Stankowski, Maciej Peksa, Marcin Nawotka, Ryszard Stanislawski, Romuald Cichon. Timing Strategy of Preoperative Aspirin and Its Impact on Early Outcomes in Patients Undergoing Coronary Artery Bypass Grafting: A Propensity Score Matching Analysis. J Surg Res. 2019 Oct 11;246:251-259. doi: 10.1016/j.jss.2019.09.026. [Epub ahead of print].

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Timing Strategy of Preoperative Aspirin and Its Impact on Early Outcomes in Patients Undergoing Coronary Artery Bypass Grafting: A Propensity Score Matching Analysis

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ABSTRACT

Background: Data are lacking regarding optimal discontinuation time of preoperative aspirin before coronary artery bypass grafting (CABG). We aimed at assessing the impact of aspirin discontinuation according to time intervals before CABG and its influence on early postoperative outcomes.

Methods: In this retrospective study, we enrolled 652 patients who underwent primary isolated nonemergent CABG between October 2014 and December 2017. Patients were assigned into groups according to the time interval between the last aspirin dose administration and the time of surgery. The first group comprised patients who were given aspirin ≤24-h before CABG ($n = 304$), whereas the second group consisted of patients who took aspirin between 24 and 48 h before CABG ($n = 348$). Efficacy endpoints included 30-d mortality rate, incidence of major adverse cardiac and cerebral events (MACCE) and composite rates of 30-d mortality/MACCE. Propensity score matching was used for final comparison.

Results: Overall, multivariate analysis showed that aspirin administration ≤24 h before CABG was associated with reduced 30-d mortality rate and MACCE by 75% and 57%, respectively. Before as well as after propensity score matching, multivariate analysis showed that aspirin administration ≤24-h before CABG was associated with reduced composite rates of 30-d mortality rate and MACCE by 55% and 59%, respectively. Subgroup analysis stratified by the type of surgery showed that aspirin administration ≤24-h significantly reduced composite rates of 30-d mortality/MACCE in patients after off-pump CABG.

Conclusions: Preoperative administration of aspirin ≤24-h before CABG is associated with the reduction of postoperative mortality as well as MACCE. The evidence also suggests that

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aspirin administration ≤24-h is strongly associated with reduced composite rates of 30-d mortality/MACCE in patients submitted to off-pump CABG.

Introduction

Aspirin (acetylsalicylic acid) is one of therapeutic mainstays in patients suffering from coronary artery disease. The main advantage of aspirin therapy was found to lay in primary and secondary prevention of cardiovascular events.[1] It is a scientifically well-established fact that postoperative administration of aspirin within first 48 h after coronary artery bypass grafting (CABG) improves postoperative survival and reduces prevalence of cardiovascular ischemic events.[2] When administered within 6 h after CABG, it could positively affect such postoperative outcomes as saphenous vein graft patency.[3] However, the use of preoperative aspirin and the time interval required for preoperative discontinuation of aspirin remains controversial. The current available guidelines differ in their recommendations in terms of perioperative aspirin use before CABG. Importantly, the latest guidelines on perioperative medications in cardiac surgery recommend continuation of aspirin until the day of surgery.[4,5] While other guidelines praise its discontinuation at least few days before elective CABG to decrease the possibility of postoperative bleeding.[6] Therefore, the current use of preoperative aspirin in patients before CABG is left mainly at the discretion of cardiac surgeon. A recent meta-analysis emphasized the importance of preoperative, low-dose aspirin which was found to be associated with decrease in mortality rate and incidence of perioperative myocardial infarction (MI) after CABG. Although it was found to benefit patients after surgical revascularization, preoperative aspirin increased the risk of postoperative bleeding but without an increase in the need for chest re-exploration or red blood cell transfusions when low-dose aspirin was maintained.[7] Interestingly, in most of the studies examining the effect of preoperative aspirin on patients submitted to CABG, the time of discontinuation of aspirin varied between 1 and 6 d preoperatively. Owing to discontinuation time variation between these studies, none of the available meta-analyses were able to examine the effect of the time interval between aspirin withdrawal and CABG. Recent studies showed that platelet function gradually normalizes within 72 h reaching full recovery within 96 h after aspirin withdrawal.[8,9] Therefore, cessation of aspirin few days before CABG could lead to partial if not complete recovery of platelet function. That in turn might lead to an increased risk of thrombotic and ischemic events in the postoperative period. Therefore, continuation of aspirin until the day of surgery could, in theory, improve postoperative outcomes and validate observation provided by Deng *et al*,[10] who showed that continuation of aspirin within 24 h of CABG is associated with the reduced mortality. On the other hand, most of the available studies compare the effect of preoperative aspirin in patients after on-pump CABG (ONCAB) or the effect was studied in mixed populations off-pump and on-pump, where most of the patients underwent ONCAB.[11,12] Only few studies examined the effect of preoperative aspirin in patients after purely off-pump CABG (OPCAB).[13-15] Therefore, we aimed to determine the impact of discontinuation of aspirin on early postoperative outcomes according to time intervals in patients after CABG with subgroup analysis in patients after OPCAB.

Methods

Study design

In this retrospective observational trial, we collected and reviewed data of 894 patients who underwent primary isolated nonemergent CABG. Enrollment of eligible patients was performed within the period between October 2014 and December 2017 at the Department of Cardiac Surgery, Medinet Heart Center Ltd, Nowa Sol, Poland. Patients who were administered with preoperative aspirin (75 mg) 24 h or less before CABG and those who were given aspirin (75 mg) between 24 and 48 h before CABG were all included in this study. Exclusion criteria included as follows: patients who had missing or unclear preoperative medication history ($n = 40$), patients who have documented intolerance to aspirin or did not take aspirin for more than 7 d ($n = 15$), patients who did not take aspirin for more than 48 h before CABG but less than 7 d ($n = 23$), emergent CABG ($n = 4$), patients enrolled to ongoing randomized controlled trial testing antiplatelet therapy after CABG ($n = 30$), patients who underwent minimally invasive CABG ($n = 95$), and patients who took >75 mg of aspirin before CABG ($n = 35$), who were excluded because of their limited number and because of the fact that aspirin doses >100 mg is associated with increased bleeding and increased incidence of packed red blood cell (pRBC) transfusions as shown in the recent meta-analyses, adding these patients might confound the results. Therefore, we aimed to perform this study with clear-cut dose of aspirin (75 mg). Of all the enrolled, 652 patients met the inclusion criteria and were assigned to groups according to the interval between their last aspirin dose and the time of surgery: those who took aspirin ≤24 h or less before CABG ($n = 304$) and those who took aspirin between 24 and 48 h before CABG ($n = 348$). Figure 1 presents patients flow chart diagram. Of the enrolled patients, a total of 526 patients underwent OPCAB, of which 243 patients took aspirin ≤24 h before surgery and 283 patients received aspirin between 24 and 48 h before OPCAB. The study was approved by the Institutional Review Board at Medinet Heart Center and by the Bioethics Committee of Wroclaw's Medical University, Poland. An individual consent of the patient for anonymous data storage and analysis was waived by the Ethics Committee.

Study data

Patients' demographics, clinical characteristics, medications, and postoperative outcomes were retrieved from the cardiac

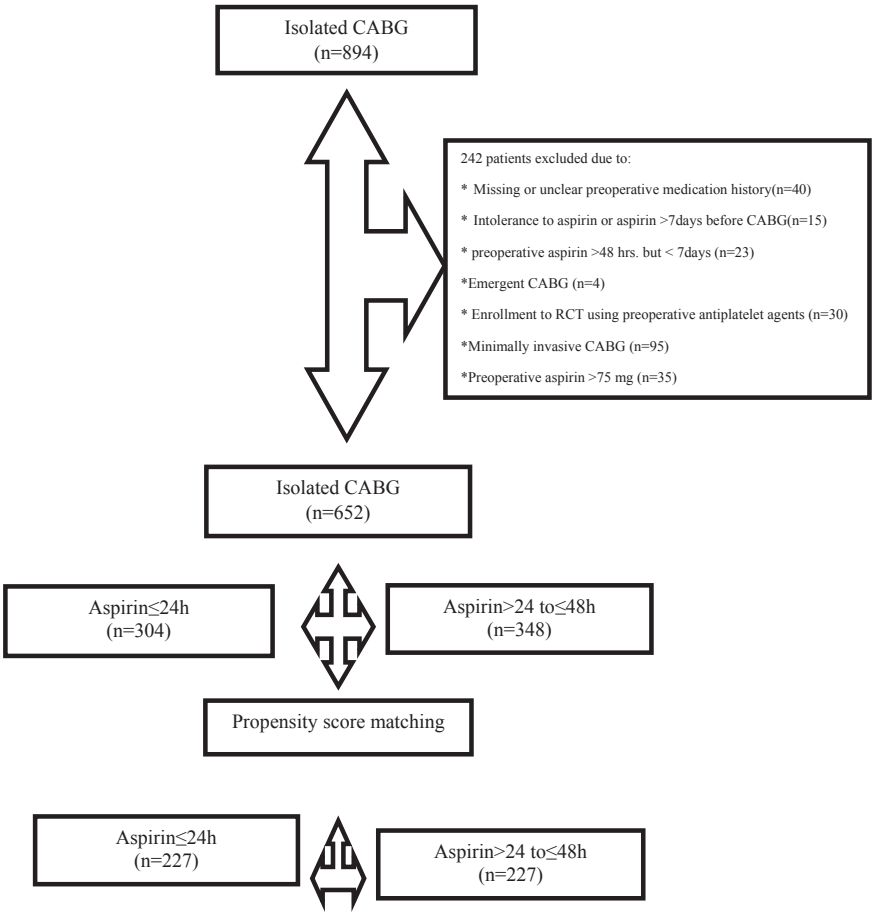

Fig. 1 – Patients flow chart diagram.

surgical database at Medinet heart Center, Nowa Sol, Poland. Dosing and timing of preoperative aspirin were obtained from patients' medication chart. The data covering preoperative dosage and time of the last aspirin dose taken by patients admitted to the hospital the day before surgery were obtained from preoperative medication questionnaire. As for patients transferred from other departments, dosage and timing of preoperative aspirin were obtained from patients' discharge letter. Postoperatively, all patients received aspirin between 12 and 24 h after CABG and that was continued daily thereafter.

Outcomes

All of the outcomes used in this study were prespecified. Efficacy endpoints included 30-d all-cause mortality, early incidence of major adverse cardiac and cerebral events (MACCE) and composite rate of 30-d mortality and MACCE. MACCE was defined as the occurrence of MI and cerebral adverse events (CAEs). MI was defined according to the third international definition of myocardial infarction.[16] CAEs were defined as development of a new permanent or transient (lasting up to 72 h) neurologic deficit as confirmed by stroke team member assessment of the patient and computed tomography, magnetic resonance imaging, or autopsy examination. Safety endpoints included postoperative chest tube drainage at t = 12 and 24 h postoperatively, postoperative transfusion rate of blood products, and incidence of postoperative re-explorations for bleeding.

Statistical analysis

All statistical analyses were performed using statistical software Statistica (TIBCO Software Inc. 2017, data analysis software system, version 13, Palo Alto). Continuous variables were expressed as means ± SD, whereas categorical variables as percentages. Having determined continuous data distribution, Student's *t* test or the Mann Whitney *U* test was used for between-groups comparisons. Categorical variables were compared with the χ^2 test or Fisher exact test. Missing data for dichotomous and continuous variables were determined with the nearest neighborhood method. Logistic regression analysis was used to identify risk factors for 30-d all-cause mortality, MACCE, and composite early mortality/MACCE. Possible preoperative risk factors in addition to operative and postoperative outcomes such as type of surgery, total arterial revascularization, number of internal thoracic arteries grafted, and blood products transfusion were identified by univariable logistic regression analysis. Then, multivariate logistic regression analysis was performed using stepwise

backward regression including only factors identified during univariate analysis at *P*-value less than or equal to 0.1. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are reported with their *P*-values. Owing to lack of randomization and to reduce any selection bias, propensity score matching (PSM) was used to match patients who took aspirin (75 mg) 24 h or less with patients who took aspirin (75 mg) between 24 and 28 h in terms of composite early mortality/MACCE in patients after CABG and OPCAB, separately. Patients were matched 1:1 between both groups using caliper matching with c = 0.001 without replacement. Propensity scores were generated from a multivariate logistic regression model based on preoperative variables. The balance of covariates between the two groups in both CABG and OPCAB was tested using standardized mean difference. After matching, the 2 groups were comparable for all confounders. Postmatching, multivariate logistic regression for composite early mortality/MACCE was again performed in the matched samples and balanced cohort. Statistical significance was defined by a *P*-value of <0.05.

Results

Between October 2014 and December 2017, 652 patients who underwent elective, primary CABG in Medinet Heart Center were included in this study. Among all patients of the cohort, 47% took aspirin (75 mg) ≤24 h before CABG and 53% discontinued it between 24 and 48 h before CABG. Overall, the 2 groups were similar with regard to age, diabetes, heart failure symptoms, decreased left ventricular function, renal insufficiency, prevalence of preoperative recent MI, and peripheral vascular disease. Female patients were more likely to be in the group where aspirin was discontinued between 24 and 48 h before CABG, whereas active smokers took aspirin more frequently ≤24 h before CABG. Concurrent preoperative medication ≤24 h such as B-blockers and statin therapy were more likely to be taken in the group of patients who took aspirin ≤24 h before CABG (Table 1).

Overall, multivariate analysis showed that aspirin administration within 24 h of CABG was independently associated

Table 1 – Demographic and clinical characteristics of patients undergoing CABG grouped according to time interval of aspirin discontinuation.

	Before matching				After matching			
	Aspirin ≤24 h (*n* = 304)	Aspirin >24 to ≤48 h (*n* = 348)	*P*	SMD	Aspirin ≤24 h (*n* = 227)	Aspirin >24 to ≤48 h (*n* = 227)	*P*	SMD
Age >70	81 (26.6)	93 (26.7)	0.98	−0.002	65 (28.6)	63 (27.7)	0.83	0.023
Female gender	62 (20.3)	103 (29.5)	0.007	−0.27	52 (22.9)	50 (22.0)	0.82	0.027
PVD	71 (23.3)	75 (21.5)	0.58	0.057	45 (19.8)	51 (22.4)	0.49	−0.087
Obesity (BMI ≥30)	105 (34.5)	132 (37.9)	0.36	−0.08	77 (33.9)	80 (35.2)	0.76	0.032
LVEF <50%	115 (37.8)	117 (33.6)	0.26	0.10	79 (34.8)	77 (33.9)	0.84	0.021
History of CAEs	33 (10.8)	31 (8.9)	0.40	0.12	23 (10.1)	25 (11.0)	0.76	−0.051
Diabetes	105 (34.5)	131 (37.6)	0.41	−0.071	80 (35.2)	78 (34.3)	0.84	0.021
Diabetes on insulin	55 (18.0)	64 (18.3)	0.92	−0.011	40 (17.6)	40 (17.6)	1	0.000
NYHA class III/IV	37 (12.1)	32 (9.1)	0.21	0.17	12 (5.2)	13 (5.7)	0.83	−0.046
Recent MI (<90 d)	119 (39.1)	135 (38.7)	0.92	0.008	85 (37.4)	93 (40.9)	0.44	−0.081
Urgent surgery	178 (58.5)	205 (58.9)	0.92	−0.008	131 (57.7)	126 (55.5)	0.63	0.049
Previous PCI	84 (27.6)	90 (25.8)	0.61	0.049	66 (29.0)	64 (28.1)	0.83	0.023
Hypertension	284 (93.4)	325 (93.3)	0.98	0.002	211 (92.9)	212 (93.3)	0.85	−0.038
Hyperlipidemia	198 (65.1)	220 (63.2)	0.61	0.045	147 (64.7)	144 (63.4)	0.76	0.031
Active smoker	120 (39.4)	107 (30.7)	0.01	0.21	74 (32.5)	73 (32.1)	0.92	0.011
≥3-vessel disease	215 (70.7)	258 (74.1)	0.33	−0.094	161 (70.9)	169 (74.4)	0.39	−0.097
Renal insufficiency	168 (55.2)	209 (60.0)	0.21	−0.108	133 (58.5)	133 (58.5)	1	0.000
Preoperative medications ≤24 h								
B-blockers	211 (69.4)	201 (57.7)	0.002	0.27	151 (66.5)	148 (65.1)	0.76	0.032
RAASI	93 (30.5)	100 (28.7)	0.60	0.049	72 (31.7)	73 (32.1)	0.91	−0.011
Statins	243 (79.9)	234 (67.2)	0.0003	0.36	179 (78.8)	180 (79.2)	0.90	−0.014
Clopidogrel ≤7 d	37 (12.1)	49 (14.0)	0.39	−0.092	25 (11.0)	29 (12.7)	0.56	−0.092

Data are expressed as *n* (%).
BMI = body mass index; CAEs = cerebral adverse events; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; RAASI = renin-angiotensin-aldosterone inhibitors; SMD = standardized mean difference.

Table 2 – Multivariate analysis: risk factors for 30-d mortality and MACCE in patients after CABG.

Variable	30-d mortality		30-d MACCE	
	OR (95% CI)	P	OR (95% CI)	P
History of CAEs			2.88 (1.27-6.53)	0.01
Active smoker			3.07 (1.62-5.83)	0.001
Renal insufficiency	11.09 (1.44-85.0)	0.021		
≥3-vessel disease			3.14 (1.19-8.29)	0.021
Aspirin ≤24 h	0.25 (0.07-0.91)	0.036	0.43 (0.22-0.85)	0.016
pRBC transfusions	1.27 (1.13-1.44)	0.000	1.20 (1.09-1.32)	0.000

with the reduction of 30-d mortality by 75% (OR: 0.25; 95% CI, 0.07-0.91; $P = 0.036$). Other significant predictors of 30-d mortality was renal insufficiency (OR: 11.09; 95% CI, 1.44-85.0; $P = 0.021$) as well as pRBC transfusions (OR: 1.27; 95% CI, 1.13-1.44; $P = 0.000$) (Table 2). In addition, multivariate analysis showed that preoperative aspirin within 24 h before CABG significantly reduced the incidence of MACCE by 57 % (OR: 0.43; 95% CI, 0.22-0.85; $P = 0.016$). Active smoking, previous CAEs, ≥3-vessel disease, and pRBC transfusions were all found to be significant predictors for an increased incidence of MACCE (Table 2). Neither were there significant differences between both groups in terms of operative outcomes such as type of surgery, number of internal thoracic grafts used, and total arterial revascularization nor in terms of safety outcomes such as postoperative bleeding, blood transfusions, and reoperation for bleeding (Table 3).

The effect of preoperative aspirin on the composite rate of 30-d/MACCE in patients undergoing CABG was studied separately. To reduce any selection bias, PSM was used to match patients who took aspirin (75 mg) ≤24 h with patients who took aspirin (75 mg) between 24 and 48 h. After matching, there were no difference between both groups with regard to preoperative variables in patients after CABG (Table 1). Before matching, multivariate analyses showed that aspirin within 24 h before CABG was independently associated with the reduction of composite rates of 30-d mortality/MACCE by 55% (OR: 0.45; 95% CI, 0.24-0.85; $P = 0.014$) (Table 4). After matching, aspirin within 24 h before CABG still reduced independently composite rates of 30-d mortality/MACCE by 59% (OR: 0.41; 95% CI, 0.19-0.88; $P = 0.02$) (Table 4). Previous CEAs, active smokers, renal insufficiency, urgent surgery, and pRBC transfusion were all risk factors for acquiring composite

Table 3 – Operative characteristics and postoperative outcomes after CABG.

	Before matching			After matching		
	Aspirin ≤24 h ($n = 304$)	Aspirin >24 to ≤48 h ($n = 348$)	P	Aspirin ≤24 h ($n = 227$)	Aspirin >24 to ≤48 h ($n = 227$)	P
Type of surgery:						
OPCAB	243 (79.9)	283 (81.3)	0.65	183 (80.6)	190 (83.7)	0.39
ONCAB	61 (20.0)	65 (18.6)	0.65	44 (19.3)	37 (16.2)	0.39
Number of ITA's used/ patient:						
1	222 (73.0)	241 (69.2)	0.28	169 (74.4)	160 (70.4)	0.34
2	77 (25.3)	99 (28.4)	0.37	56 (24.6)	64 (28.1)	0.39
Total arterial revascularization	67 (22.0)	84 (24.1)	0.52	52 (22.9)	53 (23.3)	0.91
Reoperation for bleeding	17 (5.5)	13 (3.7)	0.26	12 (5.2)	5 (2.2)	0.09
pRBC transfusion (units)	1.48 ± 2.20	1.6 ± 2.58	0.52	1.47 ± 2.04	1.43 ± 2.4	0.84
FFP or platelets transfusions (units)	0.94 ± 2.72	1 ± 3.45	0.77	0.78 ± 2.54	0.78 ± 3.02	1
Postoperative drainage at t = 12 h (mL)	425 ± 257	429 ± 258	0.84	404 ± 236	431 ± 237	0.22
Postoperative drainage at t = 24 h (mL)	665 ± 343	673 ± 366	0.77	638 ± 319	672 ± 327	0.26
30-d mortality	3 (0.98)	15 (4.31)	0.01	1 (0.44)	8 (3.52)	0.04
30-d MACCE	14 (4.60)	32 (9.19)	0.02	10 (4.4)	22 (9.6)	0.03
Duration of hospital stay (d)	7.03 ± 2.87	7.31 ± 3.69	0.28	6.94 ± 2.39	7.23 ± 3.9	0.34

Data are expressed as mean ± SD or *n* (%).
FFP = fresh frozen plasma; ITA = internal thoracic artery.

Table 4 – Multivariate analysis: risk factors for composite early mortality/MACCE in patients after CABG before and after matching.

Variable	Before matching		After matching	
	Multivariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
History of CAEs	2.51 (1.51-5.51)	0.021	3.47 (1.46-8.21)	0.005
Urgent surgery	2.00 (1.02-3.92)	0.043		
Active smoker	2.40 (1.30-4.45)	0.005	2.73 (1.33-5.60)	0.006
Renal insufficiency	2.09 (1.08-4.04)	0.028		
Aspirin ≤24 h	0.45 (0.24-0.85)	0.014	0.41 (0.19-0.88)	0.022
pRBC transfusions	1.21 (1.10-1.33)	0.000	1.22 (1.08-1.37)	0.001

endpoints consisting of 30-d mortality and MACCE in patients after CABG (Table 4). After PSM, a trend toward increased incidence of reoperation for bleeding was observed in patients who took aspirin within 24 h before CABG ($P = 0.09$) (Table 3).

Subgroup analysis in patients after OPCAB was performed with PSM. Multivariate analysis before matching showed that aspirin within 24 h before OPCAB was independently associated with reduced composite rates of 30-d mortality/MACCE by 63% (OR: 0.37; 95% CI, 0.17-0.80; $P = 0.012$) (Table 6). After matching, there was no difference between both groups with regard to preoperative risk factors (Table 5). After matching, aspirin within 24 h still reduced independently composite rates of 30-d mortality/MACCE by 80% in patients after OPCAB (OR: 0.20; 95% CI, 0.07-0.55; $P = 0.002$) (Table 6).

Table 5 – Demographic and clinical characteristics of patients undergoing OPCAB grouped according to time interval of aspirin discontinuation.

	Before matching				After matching			
	Aspirin ≤24 h ($n = 243$)	Aspirin >24 to ≤48 h ($n = 283$)	P	SMD	Aspirin ≤24 h ($n = 193$)	Aspirin >24 to ≤48 h ($n = 193$)	P	SMD
Age >70	63 (25.9)	74 (26.1)	0.95	−0.006	51 (26.4)	52 (26.9)	0.90	−0.014
Female gender	52 (21.3)	80 (28.2)	0.07	−0.20	44 (22.7)	47 (24.3)	0.71	−0.047
PVD	59 (24.2)	58 (20.4)	0.29	0.12	36 (18.6)	40 (20.7)	0.60	−0.07
Obesity (BMI ≥30)	90 (37.0)	108 (38.1)	0.79	−0.026	69 (35.7)	73 (37.8)	0.67	−0.049
LVEF <50%	88 (36.2)	90 (31.8)	0.28	0.108	66 (34.1)	63 (32.6)	0.74	0.038
History of CAEs	26 (10.6)	30 (10.6)	0.97	0.005	21 (10.8)	20 (10.3)	0.86	0.03
Diabetes	82 (33.7)	108 (38.1)	0.29	−0.105	64 (33.1)	70 (36.2)	0.52	−0.075
Diabetes on insulin	47 (19.3)	55 (19.4)	0.97	−0.003	33 (17.0)	38 (19.6)	0.51	−0.095
NYHA class III/IV	30 (12.3)	24 (8.4)	0.14	0.23	14 (7.2)	14 (7.2)	1	0.000
Recent MI(<90 d)	100 (41.1)	114 (40.2)	0.83	0.019	81 (41.9)	89 (46.1)	0.41	−0.092
Urgent surgery	144 (59.2)	166 (58.6)	0.88	0.013	113 (58.5)	120 (62.1)	0.46	−0.083
Previous PCI	71 (0.29)	77 (27.2)	0.60	0.054	59 (30.5)	51 (26.4)	0.36	0.11
Hypertension	225 (92.5)	264 (93.2)	0.75	−0.058	179 (92.7)	179 (92.7)	1	0.000
Hyperlipidemia	161 (66.2)	183 (64.6)	0.70	0.038	125 (64.7)	127 (65.8)	0.83	−0.025
Active smoker	92 (37.8)	87 (30.7)	0.08	0.174	64 (33.1)	64 (33.1)	1	0.000
≥3-vessel disease	161 (66.2)	198 (69.9)	0.36	−0.094	127 (65.8)	135 (69.9)	0.38	−0.10
Renal insufficiency	138 (56.7)	164 (57.9)	0.78	−0.026	112 (58.0)	116 (60.1)	0.67	−0.047
Preoperative medications ≤24 h								
B-blockers	170 (69.9)	163 (57.5)	0.003	0.297	124 (64.2)	127 (65.8)	0.74	−0.037
RAASI	78 (32.0)	84 (29.6)	0.54	0.062	63 (32.6)	63 (32.6)	1	0.000
Statins	195 (80.2)	192 (67.8)	0.001	0.36	157 (81.3)	157 (81.3)	1	0.000
Clopidogrel ≤7 d	32 (13.1)	41 (14.4)	0.66	−0.06	25 (12.9)	29 (15.0)	0.55	−0.095

Data are expressed as *n* (%).
BMI = body mass index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; RAASI = renin-angiotensin-aldosterone inhibitors; SMD = standardized mean difference.

Table 6 – Multivariate analysis: risk factors for composite early mortality/MACCE in patients after OPCAB before and after matching.

Variable	Before matching		After matching	
	Multivariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Female gender	0.29 (0.10-0.82)	0.019		
PVD	2.56 (1.20-5.47)	0.015		
Urgent surgery			2.87 (1.04-7.89)	0.04
Previous PCI	3.00 (1.43-6.29)	0.004		
≥3-vessel disease	3.11 (1.21-7.97)	0.018		
Aspirin ≤24 h	0.37 (0.17-0.80)	0.012	0.20 (0.07-0.55)	0.002
pRBC transfusions	1.25 (1.10-1.41)	0.000	1.18 (1.03-1.36)	0.018

PCI = percutaneous coronary intervention; PVD = peripheral vascular disease.

Comments

In this single-center, observational analysis, we found that continuation of preoperative aspirin within 24 h or less before CABG is safe and associated with reduced 30-d mortality, postoperative prevalence of MACCE, and composite rate of 30-d mortality/MACCE. This effect was particularly evident in patients after OPCAB, in whom preoperative aspirin within 24 h or less before surgery reduced composite rate of 30-d mortality and MACCE. This outcome was found significant before as well as after PSM.

Data are inconsistent regarding the optimal discontinuation time of preoperative aspirin before CABG. The current available guidelines as well as recent meta-analyses differ in their recommendations regarding the use of preoperative aspirin before CABG.[4-7,17,18] Therefore, the current use of preoperative aspirin in patient's prior CABG is related to the cardiac surgeons' preferences.

It is commonly believed that the thrombotic and ischemic events are increased in patients after ONCAB as they might be induced by inflammatory response caused by extracorporeal circulation and its effect in promoting endothelial injury.[19] On the other hand, several studies reported hypercoagulable state and platelet hyperactivity developed after OPCAB most probably due to better preservation of coagulation factors and sustained endothelial integrity when compared with ONCAB.[20-22] Antiplatelet and anti-inflammatory effects of aspirin in the perioperative period might be responsible for the prevention of early thrombotic and ischemic events after surgical revascularization. Owing to the mechanism of irreversible inhibition of platelets' cyclooxygenase (COX), aspirin is responsible for clinically significant antiplatelet effect. The duration of aspirin's antiaggregation effect in matured platelets is determined by the rate of COX resynthesis, which in this case, full platelet replacement is needed to recover COX activity. However, there is some evidence showing that platelet function gradually normalizes within 72 h after aspirin withdrawal, reaching full recovery within 96 h.[8,9] This phenomenon could be explained by the fact that low-dose aspirin does not have the ability to completely inhibit COX in human megakaryocytes presented in the bone marrow and seems to recover within 12 h after aspirin withdrawal, which leads to the regeneration of new platelets that enter the circulation shortly after aspirin discontinuation.[23,24] Moreover, the inhibition of platelet function after administration of aspirin could potentially lead to quicker production of new platelets through a feedback controlling thrombocytopoiesis.[25] Having reiterated the aforementioned, the function of newly generated platelets in the absence of aspirin re-exposure might be foreseen to recover faster than the life span of mature platelets which is around 7 to 10 d. Therefore, a partial recovery of the platelet function could be observed as soon as 24 to 48 h after aspirin discontinuation.

In this study, we aimed at examining the effect of the time interval between the aspirin discontinuation and CABG. Patients were grouped according to the interval of their last aspirin dose and the time of surgery: those who took aspirin 24 h or less before CABG and those who took aspirin between 24 and 48 h before CABG. We showed that aspirin within 24 h or less independently reduced early mortality. The similar result was observed by Deng *et al*.[10] Wu *et al*[14] indicated that continuation of preoperative aspirin could improve perioperative saphenous vein graft patency after OPCAB. Their findings could be explained by the fact that continuation of the preoperative aspirin until the surgery leads to a more profound inhibition of platelet COX, thereby helping in attenuation of the platelet aggregation and activation of coagulation during the postoperative period which in turn could reduce burden of postoperative thrombotic events.

Recent meta-analyses showed that continuation of preoperative aspirin until CABG is linked to the reduced mortality rate and lower incidence of perioperative MI, especially when low-dose aspirin is administered.[7,18]In the present study, partial antiplatelet inhibition, assumed in patients who took aspirin between 24 and 48 h prior the surgery, led to increase in the incidence of composite rates of early mortality and MACCE. This effect was clearly observed in patients after OPCAB, suggesting that the main benefits of preoperative aspirin are seen in patients submitted to OPCAB.

Several studies and meta-analyses showed that preoperative aspirin is associated with increased risk of postoperative

bleeding and increased rates of blood product transfusions. Nevertheless, at low dose, preoperative aspirin was associated with a less pronounced effect on postoperative bleeding without increasing the rates of surgical re-exploration or blood product transfusions.[7,12,18] In this study, there was neither significant difference between both groups in terms of postoperative bleeding, nor in terms of blood products transfusions in patients after CABG. However, after PSM, a trend toward increased incidence of reoperation for bleeding was observed in patients who took aspirin ≤24 h before CABG.

The present study has several limitations. First, this was a single-center, retrospective study with no preoperative randomization. It is important to acknowledge the fact that to correct the inherently high risk of bias associated with the retrospective character of our analysis, we used PSM. However, despite its use, many factors may still affect the outcomes. Second, we were unable to adjust for antifibrinolytic agents because of systematic lack of its reporting. Finally, we are aware that this study might be underpowered by the sample size. Therefore, large multicenter, randomized controlled studies are required to obtain high-level evidence guiding surgeons in optimal timing strategy of the use of preoperative aspirin before CABG.

In conclusion, preoperative aspirin within 24 h or less seems safe and is independently associated with reduced 30-d mortality rate as well as MACCE after CABG. The evidence also suggests that aspirin within 24 h or less was specifically associated with reduced composite rates of early mortality and MACCE in patients after OPCAB.

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Authors' contributions: S.S.A-H. contributed to study conception, study design, development and methodology, collection of data, data analysis and interpretation, and writing the manuscript. T.S. contributed to study design, collection of data, and manuscript revision. J.M. contributed to methodology and manuscript revision. M.P., M.N., R.S., and R.C. revised the manuscript.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Publikacja A.3

Journal of Cardiac Surgery

THE USE OF PREOPERATIVE ASPIRIN IN CARDIAC SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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REVIEW ARTICLE

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The use of preoperative aspirin in cardiac surgery: A systematic review and meta-analysis

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Abstract

Background: Despite the fact that aspirin is of benefit to patients following coronary artery bypass grafting (CABG), continuation or administration of preoperative aspirin before CABG or any cardiac surgical procedure remains controversial. Therefore, we performed a systematic review and meta-analysis to assess the influence of preoperative aspirin administration on patients undergoing cardiac surgery.

Materials and Methods: Medline database was searched using OVID SP interface. Similar searches were performed separately in EMBASE, PubMed, and Cochrane Central Registry of Controlled Trials.

Results: Twelve randomized controlled trials and 28 observational studies met our inclusion criteria and were included in the meta-analysis. The use of preoperative aspirin in patients undergoing CABG at any dose is associated with reduced early mortality as well as a reduced incidence of postoperative acute kidney injury (AKI). Low-dose aspirin (≤160 mg/d) is associated with a decreased incidence of perioperative myocardial infarction (MI). Administration of preoperative aspirin at any dose in patients undergoing cardiac surgery increases postoperative bleeding. Despite this effect of preoperative aspirin, it did not increase the rates of surgical re-exploration due to excessive postoperative bleeding nor did it increase the rates of packed red blood cell transfusions (PRBC) when preoperative low-dose aspirin (≤160 mg/d) was administered.

Conclusions: Preoperative aspirin increases the risk for postoperative bleeding. However, this did not result in an increased need for chest re-exploration and did not increase the rates of PRBC transfusion when preoperative low-dose (≤160 mg/d) aspirin was administered. Aspirin at any dose is associated with decreased mortality and AKI and low-dose aspirin (≤160 mg/d) decreases the incidence of perioperative MI.

KEYWORDS

cardiac surgery, coronary artery disease, outcomes, preoperative aspirin

1 | INTRODUCTION

Aspirin (acetylsalicylic acid, ASA) is one of the most frequently used drugs in patients with cardiovascular disease. The use of aspirin within 48 h following coronary artery bypass grafting (CABG) was found to be associated with a marked reduction of postoperative mortality and ischemic events.[1] Early postoperative administration of aspirin was also associated with a decreased risk of graft occlusion.[2] Despite the fact that aspirin is of benefit to patients following CABG, continuation or administration of preoperative aspirin before CABG or any cardiac surgical procedure remains controversial. The 2011 American College of Cardiology Foundation/American Heart Association Guidelines for Coronary Artery Bypass Surgery recommends that preoperative aspirin at a dose of 100-325 mg/d should be continued or administered before CABG since it has been shown to reduce postoperative mortality and morbidity (class I recommendation).[3] On the other hand, the Society of Thoracic Surgeons Guidelines on "Use of antiplatelet drugs in patients having cardiac and noncardiac operations" suggest that discontinuation of preoperative aspirin therapy before purely elective operations and in high-risk patients is reasonable to decrease the risk of bleeding.[4] Several observational studies showed that preoperative aspirin might improve outcomes not only in patients undergoing CABG but also in patients undergoing any other cardiac surgical procedures.[5–8] Therefore, we performed a systematic review and meta-analysis to assess the influence of preoperative aspirin administration on patients undergoing all types of cardiac surgery.

2 | METHODS

2.1 | Search strategy

Two authors (SSA and TS) independently searched the MEDLINE database for all eligible studies from 1950 to June 2017 using the OVID SP interface. Search terms were used alone or in different combinations and included: preoperative ASA or aspirin, cardiac surgery, CABG, coronary artery bypass grafting, OPCAB, survival, mortality, bleeding, drainage, reoperation for bleeding, myocardial infarction. Similar searches were performed separately by the same reviewers in EMBASE, PubMed, and Cochrane Central Registry of Controlled Trials. Any disagreement was resolved between all authors. References from all retrieved studies were crosschecked, and the "related citations" function was also used in Pubmed to further broaden the data retrieval (Figure 1).

2.2 | Inclusion criteria and data extraction

Studies were found eligible and were included in the analysis if they met the following standards: (a) randomized controlled trials (RCTs) or observational studies; (b) patients above the age of 18 years; (c) patients undergoing any type of cardiac surgery; (d) patients receiving aspirin prior to cardiac surgery or discontinuing aspirin less than 7 days prior to the surgery versus no aspirin, placebo, or discontinuation of aspirin greater than 7 days; and (e) studies submitting efficacy or safety outcomes. Endpoints such as all-cause 30-day postoperative mortality, a perioperative myocardial infarction (MI) rate, and postoperative acute kidney injury (AKI) rates were all defined as efficacy outcomes. MI in the included studies was defined as following: according to the third international definition of myocardial infarction[9] in three studies,[8,10,11] development of a new pathologic Q wave or elevated ST segments with or without elevated cardiac biomarkers values in three studies,[12–14] new ischemic electrocardiogram changes in three studies,[5,15,16] and not defined in three studies.[6,17,18] AKI in the included studies was defined as following: doubling of the serum creatinine in the postoperative period when compared with the baseline (preoperative) value or by a rise >2.4 mg/dL from baseline in one study,[10] according to KDIGO Criteria[19] in one study,[20] according to AKIN criteria[21] in one study,[6] and increase in serum creatinine more than 2.0 mg/dL and two times most recent preoperative creatinine level over baseline or new requirement for dialysis postoperatively in two studies.[8,11] Endpoints such as a packed red blood cell transfusion (PRBC) rate, postoperative bleeding, and reoperation for bleeding were all defined as safety outcomes. Studies reporting in any other language than English and those using propensity score or case-control matching were excluded. All studies or study subgroups receiving any other antiplatelet therapy or anticoagulation other than perioperative heparin were excluded from this study.

Data were extracted by the two authors (SSA and TS) independently. Baseline characteristics, study design, methodological quality, aspirin dosing, use of antifibrinolytics, and efficacy and safety outcomes were analyzed in all included studies. Any disagreement was settled between all authors. Papers that duplicated findings derived from one study group were further assessed and the most representative report was included for the analysis. The corresponding authors of the included studies were contacted on occasion if any missing or additional data were required.

2.3 | Statistical analysis

Meta-analysis was performed in agreement with the PRISMA Statement[2] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Cochrane Collaboration Guidelines for systematic reviews.[22] STATISTICA (data analysis software system), version 12, 2014 (TIBCO Software, Inc., Palo Alto, CA) and Review Manager (RevMan) (computer program), version 5.3, 2014 (The Nordic Cochrane Centre/The Cochrane Collaboration, Copenhagen, Denmark) were used to perform the meta-analysis. Mean difference was used to present the magnitude and the direction of the effect computed from continuous data as all data were expressed on the same scale, whereas odds ratio (OR) was provided for dichotomous data. DerSimonian and Laird models of random-effect were used when I^2 statistic exceeded 25%, as it allows for a greater margin of variance between studies. All outcomes are accompanied by a 95% confidence interval (CI). Statistical significance was assumed at $P < 0.05$.

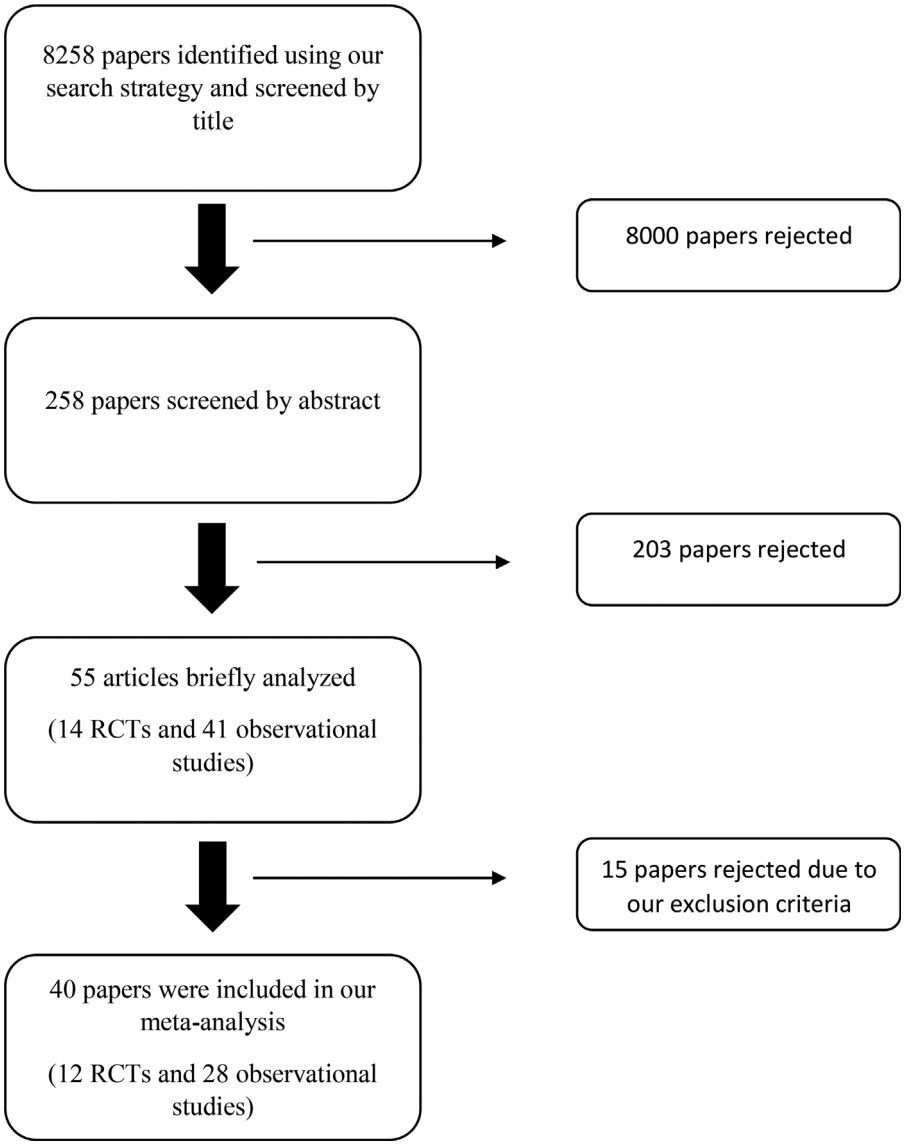

FIGURE 1 Flow chart for articles search. RCTs, randomized controlled trials

3 | RESULTS

3.1 | Characteristics of the studies

A total of 3922 patients from 12 RCTs[10,12–17,23–27] and 30 893 patients coming from 28 observational studies[5–8,11,20,28–48] met our inclusion criteria and were included in the meta-analysis. Characteristics of the studies are presented in Tables 1 and 2.

All patients included in the RCTs underwent CABG, whereas in the included observational studies 80.7% of the patients underwent CABG (n = 24 957), 8.76 % of the patients underwent valve surgery (n = 2708), 7.40% of the patients underwent concomitant CABG + valve surgery (n = 2289), and the remaining underwent other cardiac procedures 3.03% (n = 939). As a result, the majority of the patients involved in this study underwent CABG with or without heart valve surgery (89.52%). Aspirin doses varied between 75 mg/day and 2600 mg/day. After pooling all aspirin doses in a primary analysis, we intended to verify several outcomes such as postoperative bleeding and perioperative MI according to aspirin dosage. Therefore, we performed additional subgroup analysis based on the studies where the dose did not exceed 160 mg/day. In the RCTs, seven studies reported the aspirin doses ≤160 mg/day.[10,12–14,24,26,27] The rest of the studies reported aspirin doses >160 mg/day. Twelve observational studies reported aspirin doses ≤160 mg/day;[5,7,20,30–32,34,36–38,41,46] the rest of the studies reported the doses to be >160 mg/day or did not indicate the dosing at all.

3.2 | Quality of the studies and evidence of bias

All studies found eligible for the review were divided into randomized controlled trials and observational retrospective trials. Among these RCT studies, we observed several inconsistencies

TABLE 1 Characteristics of the included RCT studies

Author Country	Demographic characteristics	Group	Jadad score[49]	Type of surgery	Aspirin dosages (mg/d)	Antifibrinolytics	Endpoints
Myles[10] Australia	Mean Age 66 Male (%) 82	Aspirin *n* = 1047 Control *n* = 1053	4/5	CABG 97% OPCAB 3%	100	Yes	Mortality MI AKI Transfusion Reoperation Drainage
Berg[14] Norway	Mean Age 61 Male (%) 83	Aspirin *n* = 12 Control *n* = 8	4/5	CABG	160	Not reported	MI Reoperation Drainage
Deja[17] Poland	Mean Age 59 Male (%) 78	Aspirin *n* = 396 Control *n* = 387	4/5	CABG 82% OPCAB 18%	300	Yes	Mortality MI Transfusion Reoperation Drainage
Ghaffarinejad[13] Iran	Mean Age 56 Male (%) 68	Aspirin *n* = 100 Control *n* = 100	1/5	CABG	80-160	Yes	Mortality MI Transfusion Reoperation Drainage
Morawski[27] Poland	Mean Age 61 Male (%) 85	Aspirin *n* = 51 Control *n* = 51	4/5	CABG	300	No	Mortality MI Transfusion Reoperation Drainage
Klein[12] Germany	Mean Age 63 Male (%) 85	Aspirin *n* = 40 Control *n* = 36	2/5	CABG	100	Yes	MI Transfusion Drainage
Kallis[16] UK	Mean Age 62 Male (%) 81	Aspirin *n* = 50 Control *n* = 50	4/5	CABG	300	Not reported	Mortality MI Transfusion Reoperation Drainage
Hockings[26] Australia	Mean Age 60 Male (%) 93	Aspirin *n* = 50 Control *n* = 52	4/5	CABG	100	Not reported	Transfusion Reoperation Drainage
Goldman[25] USA	Mean Age 60 Male (%) 100	Aspirin *n* = 176 Control *n* = 175	4/5	CABG	325	Not reported	Transfusion Reoperation Drainage
Ferraris[15] USA	Mean Age 62 Male (%) 88	Aspirin *n* = 16 Control *n* = 18	2/5	CABG	325	Yes	Mortality MI Transfusion Reoperation Drainage
Karwande[24] USA	Mean Age 63 Male (%) 71	Aspirin *n* = 14 Control *n* = 10	1/5	CABG	80	Not reported	Drainage
Fuller[23] USA	Mean Age 57 Male (%) not reported	Aspirin *n* = 21 Control *n* = 9	1/5	CABG	325-2600	Not reported	Mortality Transfusion Reoperation Drainage

AKI, acute kidney injury; CABG, coronary artery bypass grafting; MI, myocardial infarction; OPCAB, off-pump coronary artery bypass; RCT, randomized control trial.

concerning the reporting methods and the overall study design. Five out of 12 studies were in fact single-blinded. Nine out of 12 were small-sample, proof-of-concept trials. Another criterion for quality assessment used in our analysis was Jadad score calculation[49] and further stratification of the studies in two groups with high and low-risk for bias. Seven RCTs[10,14,16,17,25–27] according to Jadad score[49] were of high quality whereas five RCTs[12,13,15,23,24] were of low quality. The funnel plots did not find evidence for asymmetry in all

TABLE 2 Characteristics of the included observational studies

Author Country	Demographic characteristics	Group	Type of surgery	Aspirin dosages (mg/d)	Antifibrinolytics	Endpoints
Goldhammer[28] USA	Mean age 63 Male (%) 54	Aspirin *n* = 282 Control *n* = 206	Valve	Not reported	Not reported	Mortality Transfusion Reoperation
Hur[20] Korea	Mean age 69 Male (%) 51	Aspirin *n* = 125 Control *n* = 645	CABG (7%) Valve (59%) CABG + Valve (8.7%) Other (25.3%)	75-100	Not reported	Mortality AKI Transfusion Reoperation Drainage
Goldhammer[29] USA	Mean age 63 Male (%) 65	Aspirin *n* = 603 Control *n* = 125	CABG (54%) Valve (32.8) CABG + Valve (13%)	Not reported	Yes	Transfusion Reoperation Drainage
Deng[5] USA	Mean age not reported Male (%) 76%	Aspirin *n* = 2289 Control *n* = 543	CABG	81-325	Not reported	Mortality MI Reoperation
Yao[6] USA, China	Mean age 62 Male (%) 68	Aspirin *n* = 2407 Control *n* = 1178	CABG (48%) Valve (25%) CABG + Valve (15%) Other (12%)	Not reported	Not reported	Mortality AKI
Wu[7] China	Mean age 62 Male (%) 78	Aspirin *n* = 400 Control *n* = 182	OPCAB	100	Not reported	Mortality MI Transfusion Reoperation Drainage
Al-Lawati[30] Oman	Mean age 61 Male (%) 73	Aspirin *n* = 51 Control *n* = 58	CABG	81	Yes	Mortality Reoperation Drainage
Cao[8] USA	Mean age 61 Male (%) 71	Aspirin *n* = 1923 Control *n* = 945	CABG (51%) Valve (21.6) CABG + Valve (15.4%) Other (12%)	Not reported	Not reported	Mortality MI AKI
Cao[11] USA	Mean age 62 Male (%) 67	Aspirin *n* = 1923 Control *n* = 945	CABG$^{+/-}$ Valve	Not reported	Not reported	Mortality MI AKI
Mikkola[31] Finland	Mean agem 68 Male (%) 84	Aspirin *n* = 240 Control *n* = 619	CABG	100	Yes	Mortality Transfusion Reoperation Drainage
Hijazi[32] Jordan	Mean age 64 Male (%) 65	Aspirin *n* = 400 Control *n* = 356	CABG	100	Not reported	Transfusion Reoperation Drainage
Gulbins[18] Germany	Mean age 66 Male (%) not reported	Aspirin *n* = 2519 Control *n* = 9504	CABG	Not reported	Yes	Mortality MI Transfusion Reoperation Drainage
Kamran[33] Pakistan	Mean age 53 Male (%) 90	Aspirin *n* = 15 Control *n* = 15	CABG	Not reported	Not reported	Transfusion
Sirvinskas[34] Lithuania	Mean age 64 Male (%) 74	Aspirin *n* = 25 Control *n* = 28	CABG	100	Not reported	Drainage
Bybee[35] USA	Mean age 69 Male (%) 75	Aspirin *n* = 1316 Control *n* = 320	CABG	81-325	Yes	Mortality Reoperation
Gerrah[36] Israel	Mean age 63 Male (%) 72	Aspirin *n* = 14 Control *n* = 18	CABG	100	Not reported	Mortality Transfusion Drainage

(Continues)

TABLE 2 (Continued)

Author Country	Demographic characteristics	Group	Type of surgery	Aspirin dosages (mg/d)	Antifibrinolytics	Endpoints
Gerrah[37] Israel	Mean age 69 Male (%) 78	Aspirin *n* = 46 Control *n* = 48	CABG	100	Not reported	Mortality Transfusion Drainage
Gerrah[38] Israel	Mean age 63 Male (%) 75	Aspirin *n* = 10 Control *n* = 10	CABG	100	Not reported	Mortality Transfusion Reoperation Drainage
Ray[39] Canada	Mean age 65 Male (%) 76	Aspirin *n* = 105 Control *n* = 497	CABG	Not reported	Not reported	Transfusion
Weightman[40] Australia	Mean age 62 Male (%) 83	Aspirin *n* = 610 Control *n* = 187	CABG	Not reported	No	Mortality Transfusion Reoperation
Jakics[42] USA	Mean age 64 Male (%) 72	Aspirin *n* = 51 Control *n* = 49	CABG	325	No	Transfusion Drainage
Liu[41] Australia	Mean age 69 Male (%) not reported	Aspirin *n* = 35 Control *n* = 10	CABG	150	Not reported	Transfusion Drainage
Vuylsteke[43] UK	Mean age 61 Male (%) 81	Aspirin *n* = 86 Control *n* = 58	CABG	≤325	No	Transfusion Reoperation Drainage
Reich[44] USA	Mean age 68 Male (%) 68	Aspirin *n* = 87 Control *n* = 110	CABG	Not reported	No	Transfusion Reoperation Drainage
Rawitscher[45] USA	Mean Ag 61 Male (%) 76	Aspirin *n* = 28 Control *n* = 72	CABG	85-325	Not reported	Mortality Transfusion Reoperation Drainage
Taggart[46] Scotland	Mean age 57 Male (%) 83	Aspirin *n* = 101 Control *n* = 101	CABG	85-300	Not reported	Reoperation Drainage
Michelson[47] USA	Mean age 54 Male (%) 100	Aspirin *n* = 9 Control *n* = 16	CABG	600-2400	Not reported	Transfusion Drainage
Torosian[48] USA	Mean age 54 Male (%) 89	Aspirin *n* = 9 Control *n* = 64	CABG	600-2400	Not reported	Reoperation Drainage

AKI, acute kidney injury; CABG, coronary artery bypass grafting; MI, myocardial infarction; OPCAB, off-pump coronary artery bypass.

performed analyses. Not a single study was found to outlie the 95% CI.

3.3 | Efficacy outcomes

3.3.1 | Mortality

RCTs

Seven RCTs[10,13,15–17,23,27] reported on postoperative 30-day mortality with a total of 3362 patients. Pooling the results of RCTs, preoperative aspirin did not show any statistically significant impact on postoperative mortality (OR 1.15; 95%CI 0.65-2.04; $P = 0.62$; $I^2 = 0\%$; P heterogeneity = 0.95) (Figure 2).

Observational studies

Sixteen observational studies[5–8,11,18,20,28,30,31,35–38,40,45] reported 30-day mortality with an aggregate of 27 944 patients. Pooling the results of the observational studies, preoperative aspirin showed a significant decrease in postoperative mortality by 32% (OR 0.68; 95%CI 0.55-0.85; $P = 0.0004$; $I^2 = 23\%$; P heterogeneity = 0.19) (Figure 2).

Overall

Pooling the results of both RCTs[10,13,15–17,23,27] and observational studies,[5–8,11,18,20,28,30,31,35–38,40,45] preoperative aspirin showed a significant decrease in postoperative mortality by 29% (OR 0.71; 95%CI 0.6-0.84; $P = 0.0001$; $I^2 = 7\%$; P heterogeneity = 0.36). A total of 31 306 patients have been pooled to assess 30-day mortality of which

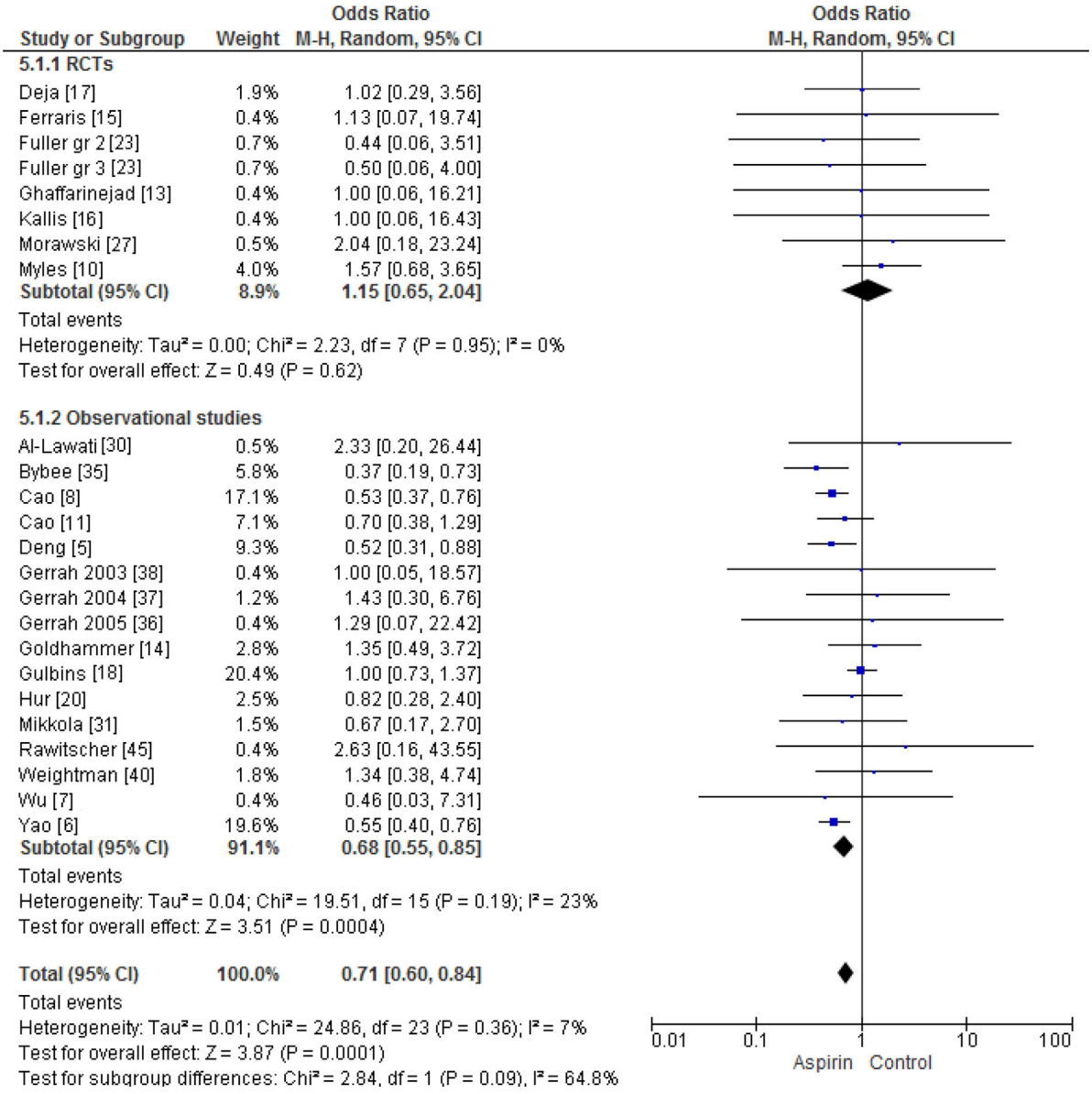

FIGURE 2 Analysis of randomized controlled trials and observational studies for early postoperative mortality in patients with preoperative aspirin versus control

93.03% underwent CABG with or without heart valve surgery (Figure 2).

3.3.2 | Perioperative myocardial infarction

RCTs

Eight RCTs[10,12–17,27] reported on the effect of preoperative aspirin on postoperative MI with a total of 3420 patients. In terms of pooling the results of RCTs only, preoperative aspirin did not show any significant effect on perioperative MI (OR 0.83; 95%CI 0.66-1.04; $P = 0.1$; $I^2 = 0\%$; P heterogeneity = 0.97) (Figure 3). Five RCTs,[10,12–14,27] consisting of 2500 patients, reported administration of aspirin doses lower or equal to 160 mg/d. In those patients, no significant effect on perioperative MI was observed (OR 0.83; 95%CI 0.66-1.06; p = 0.13; $I^2 = 0\%$; P heterogeneity = 0.63) (Figure 4).

Observational studies

Five observational[5,7,8,11,18] studies reporting the effect of preoperative aspirin on postoperative MI with a total of 20 038 patients, found no association between preoperative aspirin and perioperative myocardial infarction (OR 0.95; 95%CI 0.71-1.27; $P = 0.72$; $I^2 = 21\%$; P heterogeneity = 0.28) (Figure 3). Among those, two observational studies[5,7] reporting perioperative MI outcomes (overall 2412 patients), where the aspirin dosing was ≤160 mg/d, showed a trend towards decreased perioperative MI in patients with preoperative aspirin (OR 0.63; 95%CI 0.38-1.04; $P = 0.07$; $I^2 = 0\%$; P heterogeneity = 0.81) (Figure 4).

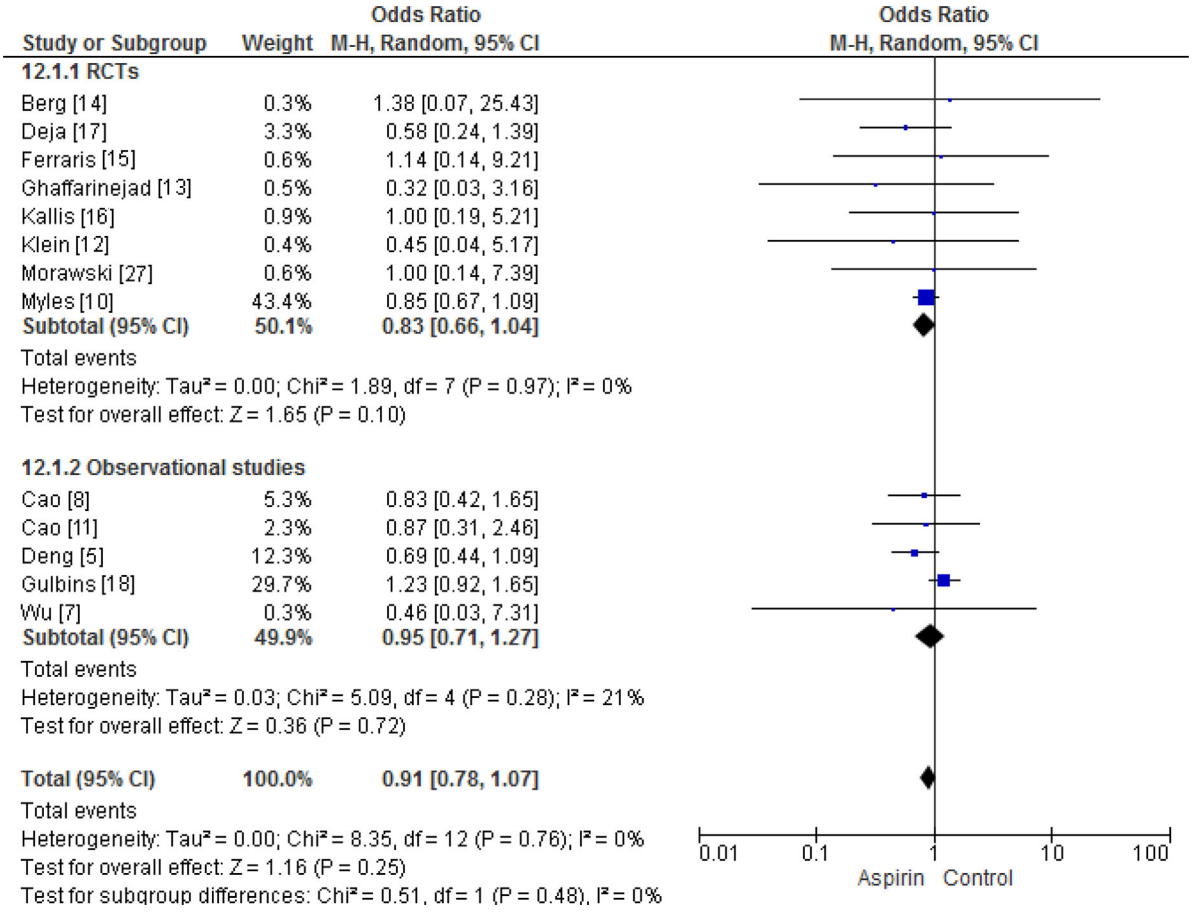

FIGURE 3 Analysis of randomized controlled trials and observational studies for postoperative myocardial infarction in patients with preoperative aspirin versus control

Overall

Pooling the results of both RCTs[11,14–20] and observational studies,[5,7,8,11,18,32] preoperative aspirin did not show any statistically significant effect on perioperative MI (OR 0.91; 95%CI 0.78-1.27; $P = 0.25$; $I^2 = 0$ %; P heterogeneity = 0.76) (Figure 3). A sum of 23, 458 patients was reported pooling the results of eight RCTs[10,12–17,27] and five observational studies[5,7,8,11,18] where 95.51% of the patients underwent CABG with or without concomitant heart valve surgery. Five RCTs[10,12–14,27] and two observational studies[5,7] reported on preoperative aspirin dosing ≤160 mg/day (4912 patients). In a low-dose preoperative aspirin group, a significant decrease by 21% in the rate of postoperative MI was noted (OR 0.79; 95%CI 0.64-0.98; $P = 0.03$; $I^2 = 0\%$; P heterogeneity = 0.73) (Figure 4). All patients in this analysis underwent CABG.

3.3.3 | Incidence of postoperative AKI

A single RCT[10] and four observational studies,[6,8,11,20] pooling evidence from 10 468 patients, reported the effect of preoperative aspirin on the incidence of postoperative AKI. Pooling the results, preoperative aspirin showed a significant decrease in the incidence of postoperative AKI by 32 % (OR 0.68; 95%CI 0.51-0.91; $P = 0.008$) Heterogeneity was significant ($I^2 = 70\%$; P heterogeneity = 0.01) (Figure 5). A total of 72.25% of the patients underwent CABG$^{+/-}$ concomitant valve surgery, and the remaining patients underwent isolated valve surgery or other cardiac procedures.

3.4 | Safety outcomes

3.4.1 | Packed red blood cell transfusion

RCTs

Ten RCTs[10,12,13,15–17,23,25–27] reported PRBC transfusion rates. The evidence was based on data derived from 3878 patients. After pooling the results, preoperative aspirin increased the rate of PRBC transfusions (MD 0.45 unit; 95%CI 0.24-0.67; $P < 0.0001$) heterogeneity was significant ($I^2 = 54\%$; P heterogeneity = 0.02) (Figure 6). In the pooled analysis, in trials using less or equal to 160 mg/d of aspirin (five RCTs[10,12,13,16,27] with a total of 2580 patients), preoperative aspirin significantly increased the rate of PRBC transfusions (MD 0.34 unit; 95%CI 0.13-0.55; $P = 0.002$; $I^2 = 19\%$; P heterogeneity = 0.29) (Figure 7).

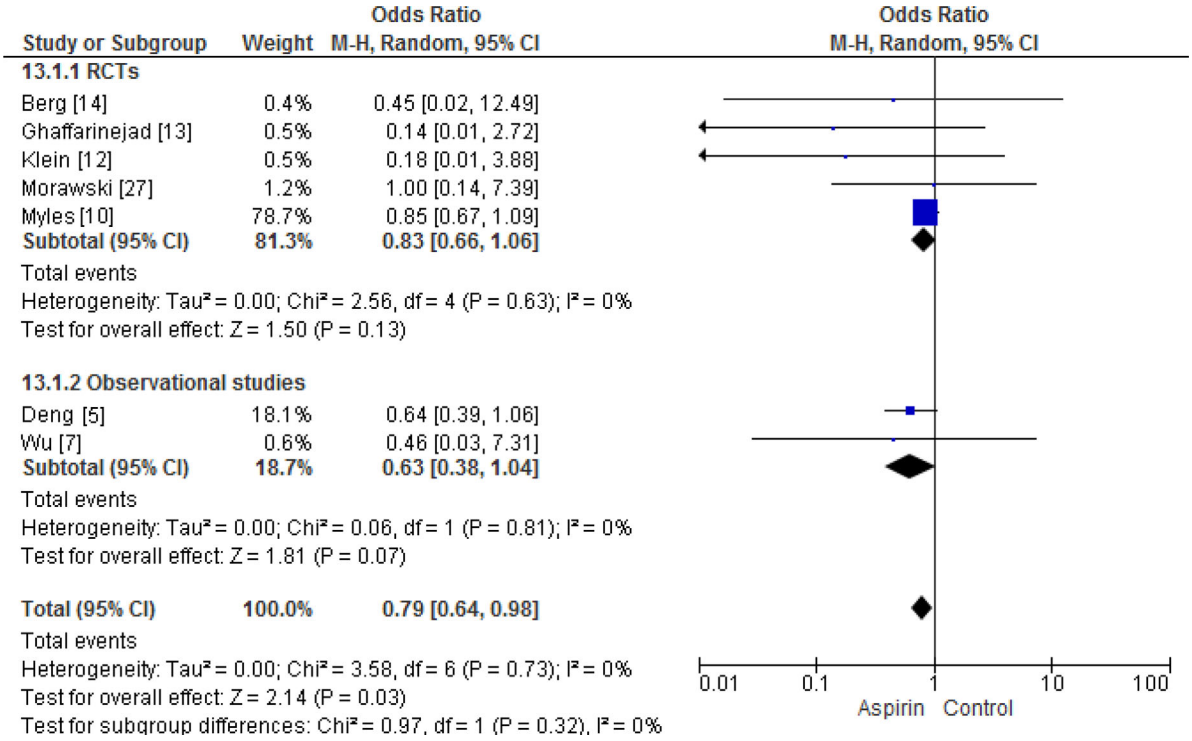

FIGURE 4 Analysis of randomized controlled trials and observational studies for postoperative myocardial infarction in patients with preoperative low-dose aspirin (≤160 mg-d) versus control

Observational studies

Nineteen observational studies[7,18,28,29,31-33,36–45,47] reported PRBC transfusion rates. The analysis was based on the results from 18 392 patients. Pooling the results, no difference was observed in the rates of PRBC transfusions (MD 0.08 unit; 95%CI −0.05 to 0.21; $P = 0.24$), although heterogeneity was found to be significant ($I^2 = 61\%$; P heterogeneity = 0.0003) (Figure 6). Eight observational studies[7,20,31,32,36–38,41] reported on the administration doses of ≤160 mg/d aspirin, with a sum of 3158 patients. The analysis showed no difference in the rates of PRBC transfusions between preoperative

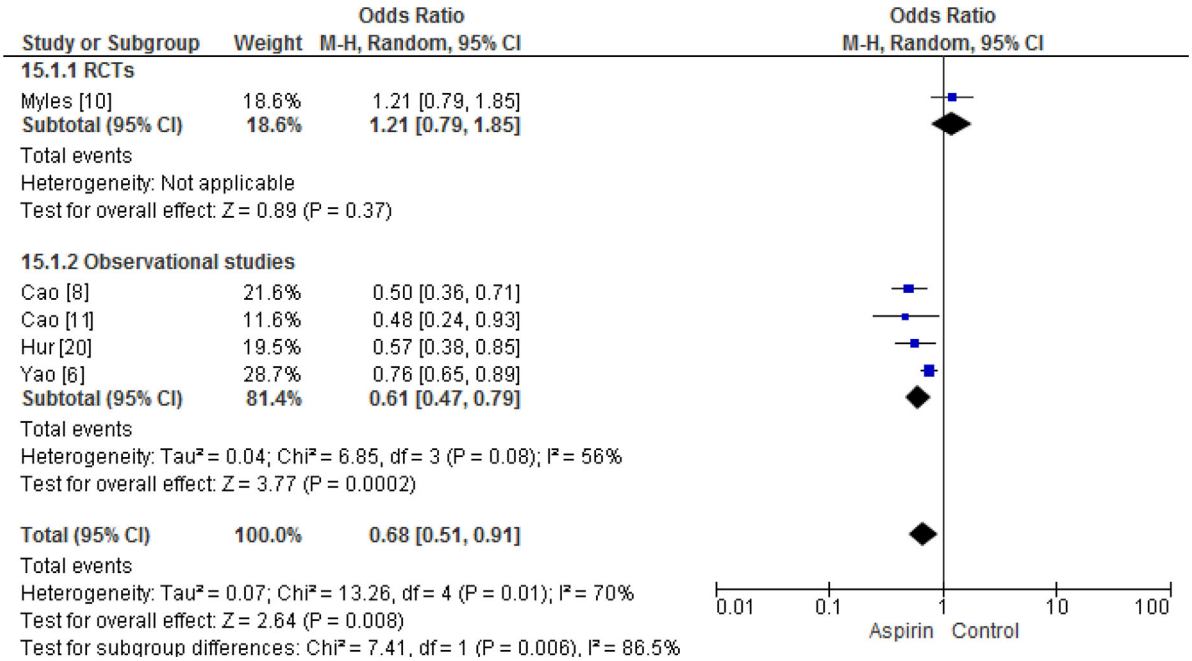

FIGURE 5 Analysis of randomized controlled trials and observational studies for postoperative acute kidney injury in patients with preoperative aspirin versus control

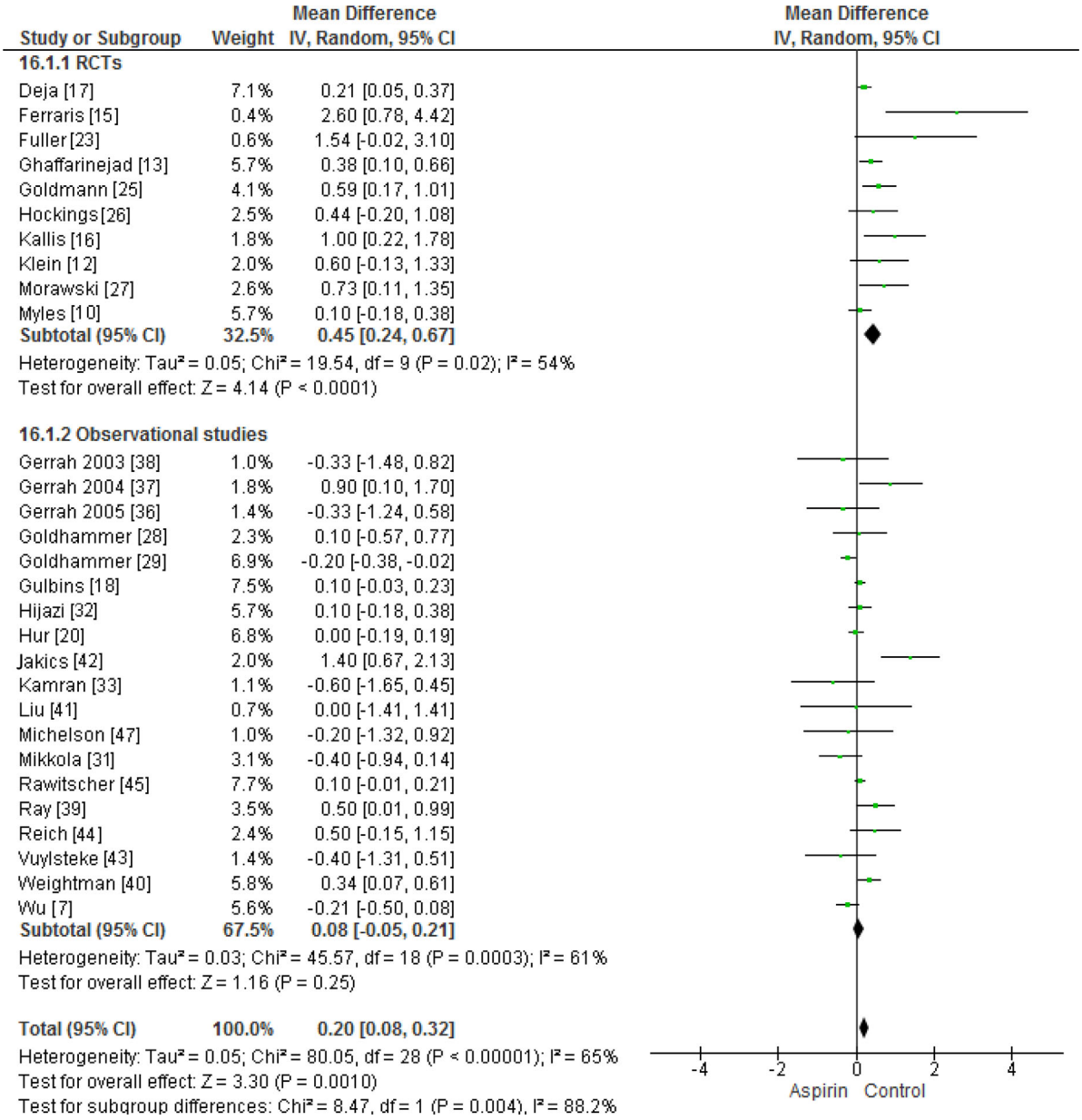

FIGURE 6 Analysis of randomized controlled trials and observational studies for packed red blood cell transfusions in patients with preoperative aspirin versus control

aspirin and placebo groups (MD −0.04 unit; 95%CI −0.23 to 0.15; $P = 0.68$; $I^2 = 31\%$; P heterogeneity = 0.18) (Figure 7).

Overall

Pooling the results of both RCTs[10,12,13,15–17,23,25–27] and observational studies,[7,20,28,29,31–34,36–45,47] preoperative aspirin increased the rate of PRBC transfusion (MD 0.20 unit; 95%CI 0.08-0.21; $P = 0.0008$) with relatively high heterogeneity ($I^2 = 65$ %; P heterogeneity < 0.00001) (Figure 6). Meta-analysis of the results of both RCTs[10,12,13,16,27] and observational studies[7,20,31,32,36–38,41] which used low-dose aspirin (≤160 mg/d) revealed no significant difference in the rates of PRBC transfusions (MD = 0.13 unit; 95%CI −0.05 to 0.31; $P = 0.15$) (Figure 7).

93.82% of the patients underwent CABG$^{+/-}$ concomitant valve surgery.

3.4.2 | Reoperation for bleeding

RCTs

Ten RCTs[10,13–17,23,25–27] reported reoperation for bleeding rates with a total of 3828 patients. Pooling the results, no statistically significant difference was observed in the rates of surgical re-exploration due to bleeding (OR 1.31; 95%CI 0.90-1.93; $P = 0.16$; $I^2 = 0\%$; P heterogeneity = 0.66) (Figure 8).

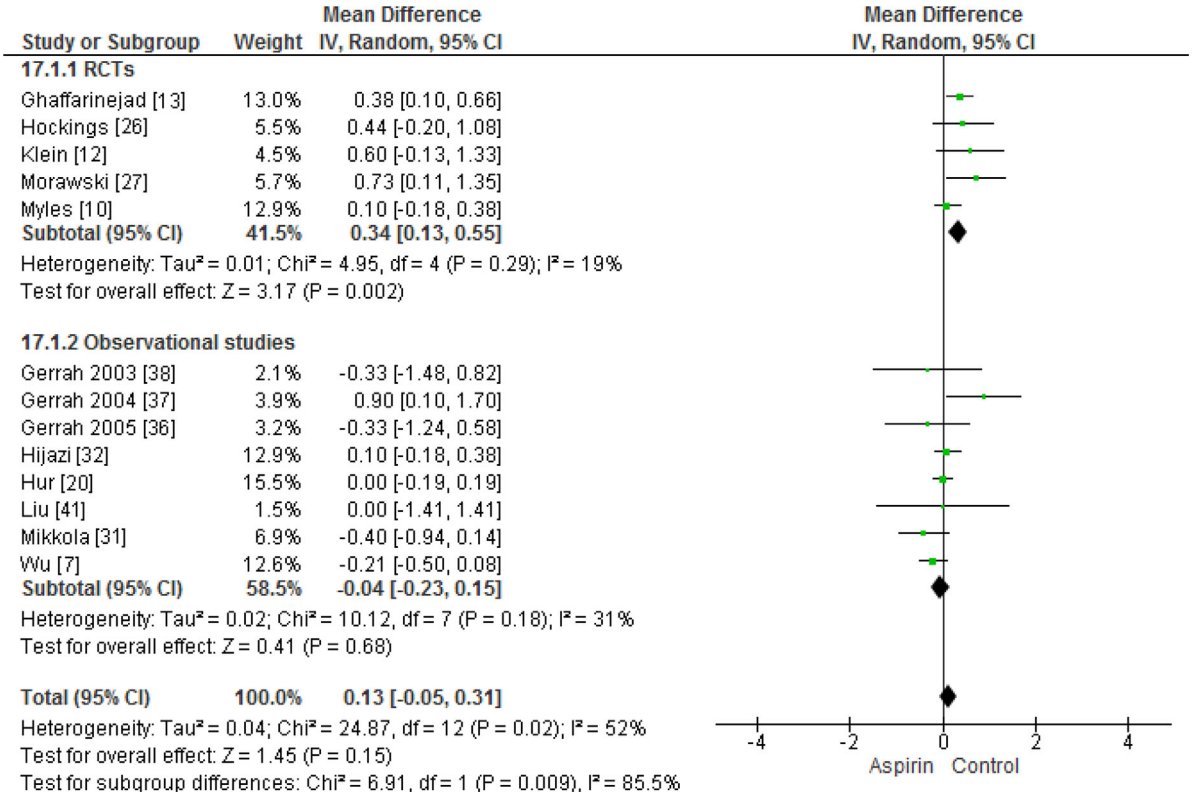

FIGURE 7 Analysis of randomized controlled trials and observational studies for packed red blood cell transfusions in patients with preoperative low-dose aspirin (≤160 mg-d) versus control

Observational studies

Seventeen observational studies[5,7,20,28,29,30–33,35,38,40,43–46,48] reported reoperation for bleeding. Pooling the results of 22 318 patients, no difference was observed in the rates of surgical re-exploration for bleeding between those receiving ASA and in whom ASA had been withdrawn preoperatively (OR 0.96; 95%CI 0.80-1.16; $P = 0.7$; $I^2 = 0\%$; P heterogeneity = 0.85) (Figure 8).

Overall

Pooling the results of both RCTs[10,13–17,23,25–17] and observational studies,[5,7,18,20,28–32,35,38,40,43–46,48] preoperative aspirin did not show any substantial difference in the rates of surgical re-exploration due to bleeding (OR 1.02; 95%CI 0.86-1.21; $P = 0.79$; $I^2 = 0$ %; P heterogeneity = 0.83) (Figure 8). The evidence was derived from the analysis of 26 146 patients, of who 94.11% underwent an isolated CABG, 0.61% underwent CABG$^{+/-}$ concomitant heart valve surgery, and 4.5% underwent valve surgery.

3.4.3 | Postoperative chest drainage

RCTs

Twelve RCTs[10,12–17,23–27] reported postoperative chest drainage in 3812 patients. Pooling the results, preoperative aspirin significantly increased postoperative chest drainage volume (MD = 111.04 mL; 95%CI 28.73-193.34; $P = 0.008$), heterogeneity was found to be significant ($I^2 = 95\%$; P heterogeneity < 0.00001) (Figure 9). Seven RCTs[10,12–14,24,26,27] reported administration of the aspirin doses of ≤ 160 mg/d with a total of 2619 patients. Low-dose preoperative aspirin did not increase postoperative chest drainage volume (MD = 23 mL; 95%CI −74.95 to 120.94; $P = 0.65$) with high heterogeneity ($I^2 = 76\%$; P heterogeneity = 0.0003) (Figure 10).

Observational studies

Eighteen observational studies[7,18,20,29,30,31,34,36–38,41–48] reported postoperative chest drainage ($n = 16\,158$ patients). Preoperative aspirin significantly increased postoperative chest drainage (MD = 155.43 mL; 95%CI 77.76-233.10; $P < 0.0001$) with heterogeneity assumed as significant ($I^2 = 95\%$; P heterogeneity < 0.00001) (Figure 9). Ten observational studies[7,20,30,31,34–38,41,46] reported administration of aspirin doses of ≤160 mg/d with an aggregate of 3180 patients. Pooling the results, preoperative low-dose aspirin significantly increased postoperative chest drainage (MD = 106.27 mL; 95%CI 51.06-161.47; $P = 0.0002$); heterogeneity was significant ($I^2 = 67\%$; P heterogeneity = 0.0008) (Figure 10).

Overall

Pooling the results of both RCTs[10,12–17,23–27] and observational studies,[7,17,19,28–30,34,36–38,41–48] preoperative aspirin significantly

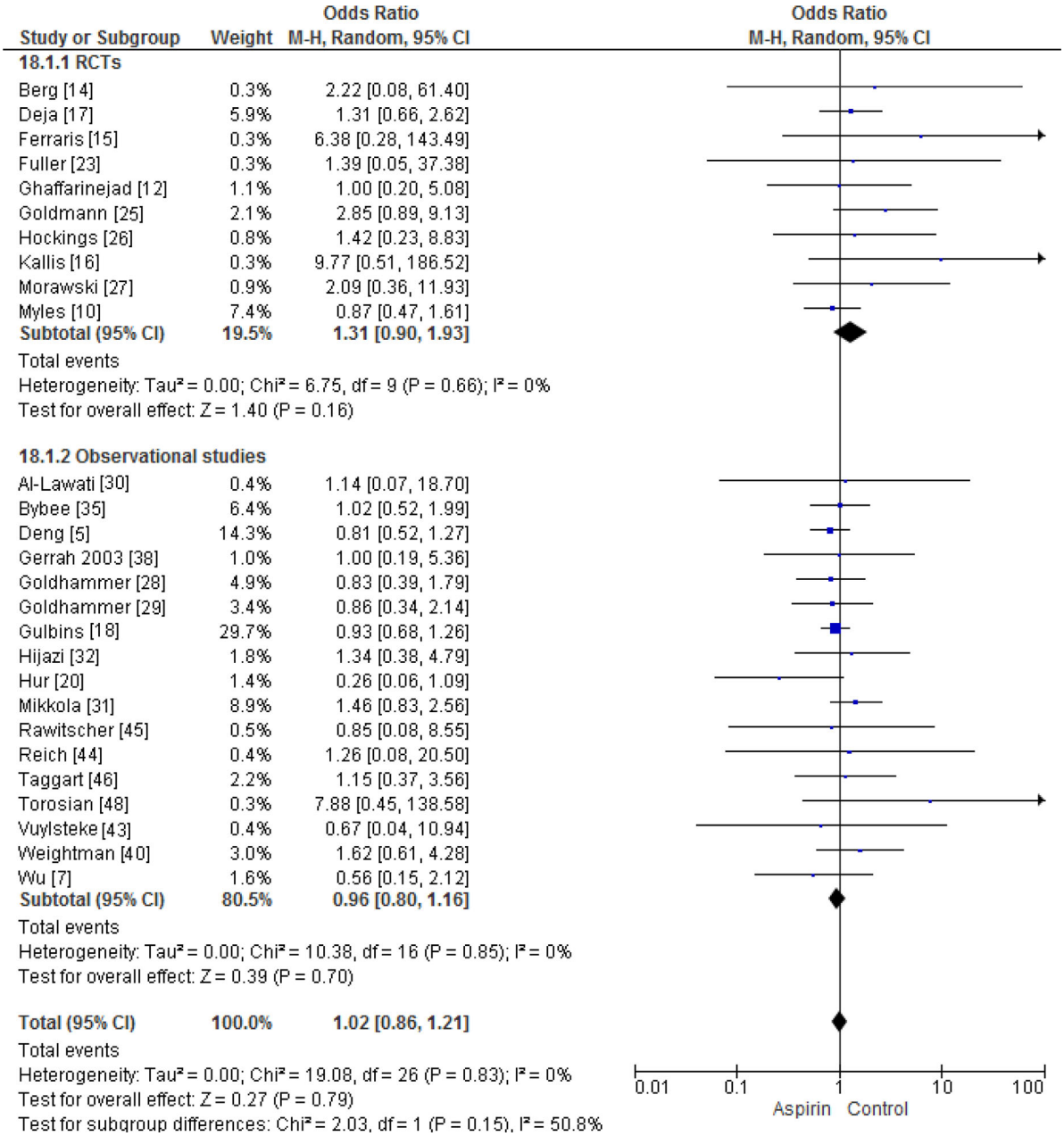

FIGURE 8 Analysis of randomized controlled trials and observational studies for reoperative for bleeding in patients with preoperative aspirin versus control

increased postoperative chest drainage (MD = 139.26 mL; 95%CI 86.92-191.59; $P < 0.00001$) with significant heterogeneity ($I^2 = 95\%$; P heterogeneity < 0.00001) (Figure 9). Low-dose aspirin preoperative pretreatment increased postoperative chest drainage volume by an average of 77.47 mL (MD = 77.47 mL; 95%CI 29.84-125.09; $P = 0.001$) and heterogeneity was found to be significant ($I^2 = 76\%$; P heterogeneity < 0.00001) (Figure 10). Evidence was derived from the analysis of 19 970 patients, of who 94.86% underwent an isolated CABG, 0.79% underwent CABG$^{+/-}$ concomitant heart valve surgery, 3.4% underwent valve surgery, and 0.95% other cardiac procedures.

4 | DISCUSSION

Aspirin has an antiplatelet effect through its irreversible inactivation of platelet cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) which inhibits the aggregation effect of the platelets and provides an anti-inflammatory effect.[50–52] This effect of aspirin on platelets reduces thrombotic risks, which is believed to be increased in patients undergoing cardiac surgery, especially in those patients undergoing on-pump CABG due to the endothelial injury and the effect of the extracorporeal circulation.[52,53] This effect has also been observed in patients undergoing off-pump CABG due to platelet hyperactivity

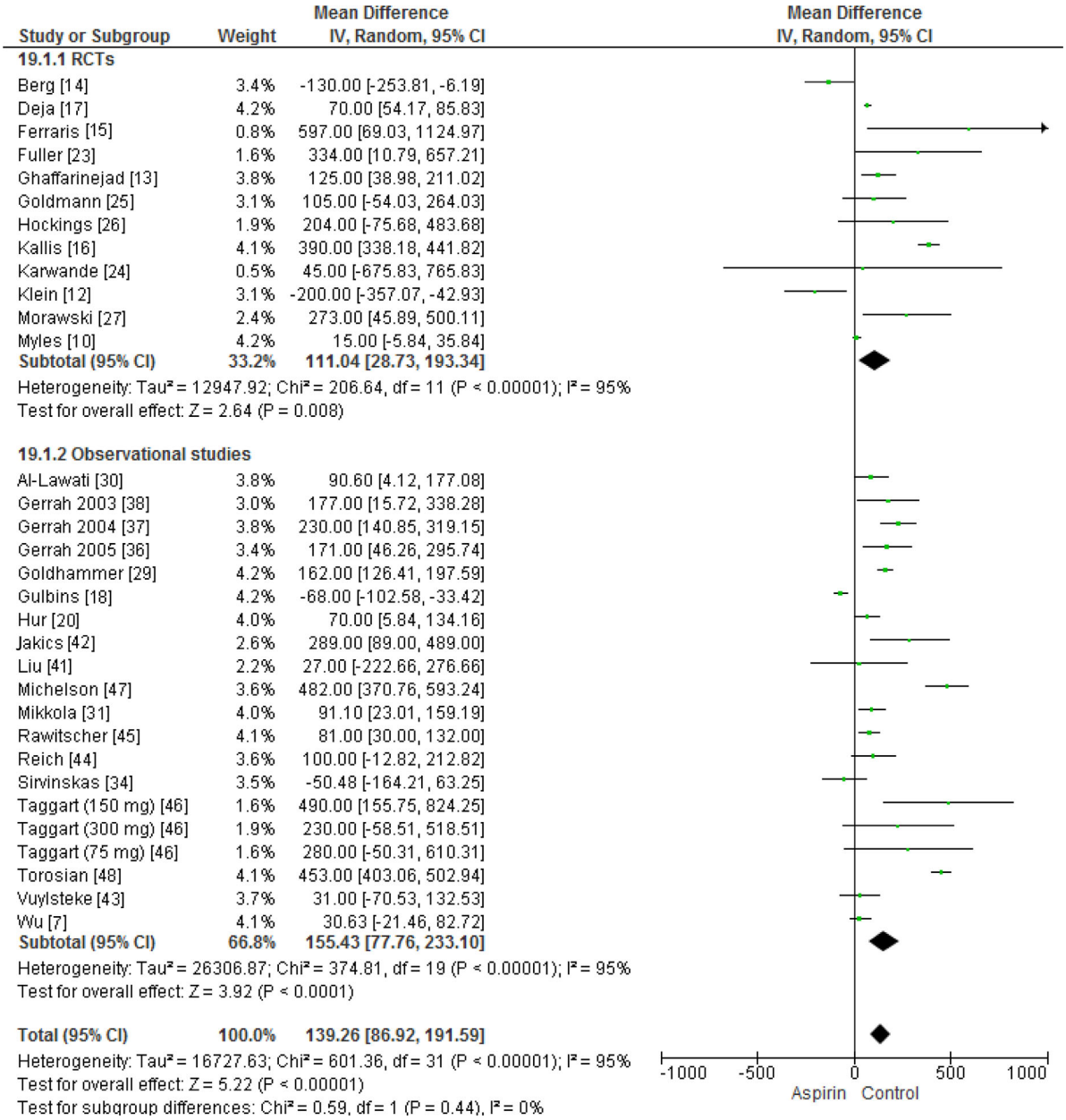

FIGURE 9 Analysis of randomized controlled trials and observational studies for postoperative chest drainage in patients with preoperative aspirin versus control

following the procedure.[50,51,55] Aspirin also provides an anti-inflammatory effect which could additionally increase its protective effects during cardiac surgery.[14,52,56–59]

The 2011 ACC/AHA Guidelines for Coronary Artery Bypass Surgery recommends that preoperative aspirin at a dose of 100 mg to 325 mg/d should be continued or administered prior to CABG since it was shown to reduce postoperative mortality and morbidity (class I recommendation).[3] Our meta-analysis demonstrated that preoperative aspirin decreased postoperative mortality by 29%. A recent meta-analysis, which consisted of RCTs, has revealed that preoperative low-dose aspirin (≤160 mg/d) decreases the incidence of perioperative MI by 44%.[57] Our results demonstrated that preoperative low-dose aspirin (≤160 mg/day) significantly reduced the incidence of perioperative MI by 21%. Several studies[6,8,11,20] showed that preoperative aspirin reduces the incidence of postoperative AKI in patients undergoing cardiac surgery. Mangano et al[1] showed that aspirin within 48 h following CABG is related to reduced postoperative mortality and lower rates of the composite outcome of cardiac, cerebral, and renal ischemic events. Our findings showed that preoperative aspirin decreased postoperative AKI by 32% in patients undergoing cardiac surgery mainly in CABG patients. This effect of preoperative aspirin could be explained by the anti-inflammatory effect of aspirin, where inflammation following ischemia-reperfusion injury was associated with an increase of postoperative incidence of AKI.[60–63]

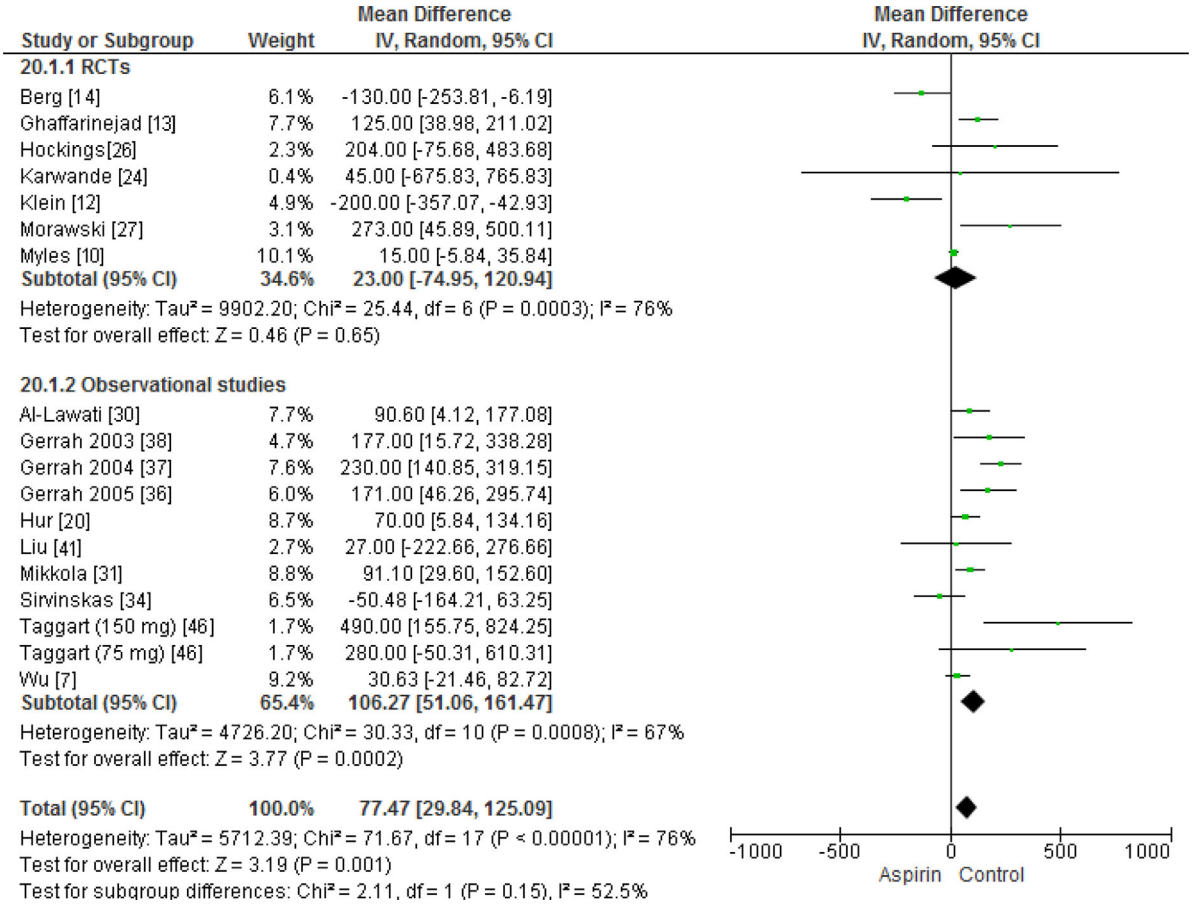

FIGURE 10 Analysis of randomized controlled trials and observational studies for postoperative chest drainage in patients with preoperative aspirin low-dose aspirin (≤160 mg-d) versus control

The STS position paper on the "Use of antiplatelet drugs in patients having cardiac and non-cardiac operations" suggests that discontinuation of preoperative aspirin therapy before purely elective operations and in high-risk patients is reasonable to decrease the risk of bleeding.[4] In our study, PRBC transfusion rates were increased when preoperative aspirin was administered in all doses. However, preoperative aspirin at a low dose (≤160 mg/d) was not associated with any statistically significant increase in the rates of PRBC transfusions. On the other hand, several studies showed that preoperative aspirin could be related to an increase in postoperative bleeding following cardiac surgery.[15–17,27,29,31,36–38,42,45,47] Others observed that this effect could be decreased or even eliminated when a low dose aspirin is administered preoperatively.[7,10,14,24,26,30,34,41,46,63] In our analysis, preoperative aspirin increased postoperative bleeding following cardiac surgery by an average of 77 mL. Subgroup analysis, according to a dose of aspirin given preoperatively, showed that even low-dose aspirin increases postoperative bleeding. Heterogeneity in both studies was statistically significant, which could be explained by the variation in the preoperative aspirin dosing. Higher postoperative chest drainage volume in patients taking preoperative aspirin correlated neither with an increase in the rates of surgical re-exploration for bleeding nor with PRBC transfusion rates, when a low dose aspirin (≤160 mg/d) was administered. Hence, while the increased chest tube output was statistically significant, it did not appear to be clinically significant.

This study highlights the effect of preoperative aspirin in patients undergoing cardiac surgery with the great majority undergoing CABG and shows that preoperative aspirin has a significant benefit in reducing early mortality, perioperative MI, and postoperative AKI with no correlation in the incidence of reoperation for bleeding and increased PRBC transfusions when low-dose aspirin was administered.

This meta-analysis has several limitations. First, we pooled the results of RCTs and observational studies of all outcomes. Although it is controversial as to whether or not to combine the results of different study designs, we believed that the enormous amount of patients provided by the observational studies should not be omitted. To resolve this issue, we have provided individual meta-analytical assessment for both study designs. Secondly, due to the nonrandomized and unblinded design of the observational studies, a potential bias could be introduced in this meta-analysis. Thirdly, heterogeneity was statistically significant in the analysis of the incidence of postoperative acute kidney failure, PRBC transfusions, and postoperative chest drainage. This heterogeneity was probably

due to variation in preoperative aspirin dosing, the use of antifibrinolytics, and timing of administration of postoperative aspirin. Fourthly, we failed to show the effect of preoperative aspirin in other than CABG procedures since the majority of the patients underwent CABG with or without concomitant valve surgery. We could not have elaborated on the effect of preoperative aspirin in patients undergoing off-pump versus on-pump CABG due to lack of studies analyzing those procedures separately. Finally, no mid-term or long-term follow-up data were available for the analysis. Therefore, it is still unknown how preoperative aspirin influences long-term clinical endpoints.

5 | CONCLUSIONS

The use of preoperative aspirin in patients undergoing CABG at any dose is associated with reduced early mortality as well as reduced incidence of postoperative AKI. Low-dose aspirin (≤160 mg/d) is associated with a decreased incidence of perioperative MI. Administration of preoperative aspirin at any dose in patients undergoing cardiac surgery increases postoperative bleeding. However, low-dose of aspirin (≤160 mg/d) is associated with a less pronounced effect on postoperative bleeding. Nevertheless, preoperative aspirin did not increase the rates of surgical re-exploration due to excessive postoperative bleeding nor did it increase the rates of PRBC transfusions when preoperative low-dose aspirin (≤160 mg/d) was administered.

Based on our results, concerns remain about the higher risk of postoperative bleeding following CABG. However, it should not dissuade patients from using preoperative low-dose aspirin as the benefits of using preoperative low-dose aspirin exceed the chance for potential complications. Therefore, we recommend that preoperative low-dose aspirin should be continued or administered before CABG.

CONFLICTS OF INTEREST

The authors have no conflicts to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Pisemne oświadczenia współautorów prac towarzyszących cykl publikacji

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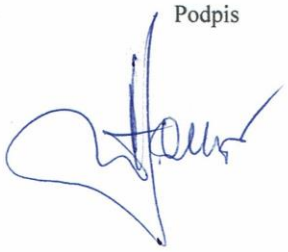

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Podpis

Lek. Maciej Pęksa
DCChS Medinet w Nowej Soli
Ul.Chałubińskiego 7
67-100Nowa Sól

Nowa Sól 21.10.2019

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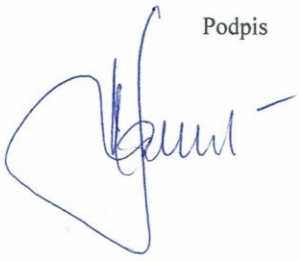

Dr n. med. Tomasz Stankowski
Sana Herzzentrum Cottbus
Leipziger Str. 50
03048 Cottbus, Niemcy

Cottbus 18.10.2019

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Podpis

Dr hab. n. med. Romuald Cichoń
Dolnośląskiego Centrum Chorób Serca
im. prof. Zbigniewa Religi
MEDINET Sp. z o.o.
ul. Kamieńskiego 73 a
51-124 Wrocław

Wrocław 18.10.2019

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Podpis

Lek. Bartosz Kryszkowski
Wojewódzkie Centrum Szpitalne Kotliny Jeleniogórskiej
Ogińskiego 6
58-506 Jelenia Góra

Jelenia Góra 09.11.2019

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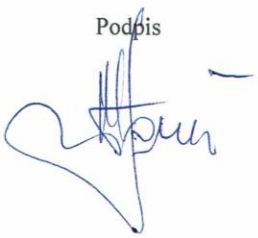

Lek. Marcin Nawotka
DCChS Medinet w Nowej Soli
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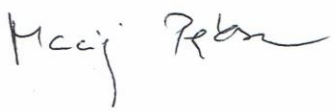

Orzeczenie Komisji Bioetycznej

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 431/2018

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

dr hab. Jacek Daroszewski (endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód (duchowny)
mgr Luiza Müller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
dr hab. Leszek Szenborn (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Wpływ stosowania przedoperacyjnego kwasu acetylosalicylowego u pacjentów poddanych chirurgicznej rewaskularyzacji naczyń wieńcowych"

zgłoszonym przez **lek. Sleimana Sebastiana Aboul-Hassana** zatrudnionego w Dolnośląskim Centrum Chorób Serca Medinet we Wrocławiu w Filii w Nowej Soli oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła wyrazić zgodę na przeprowadzenie badania w Dolnośląskim Centrum Chorób Serca Medinet we Wrocławiu w Filii w Nowej Soli pod nadzorem dr hab. Romualda Cichonia **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności:

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu

Opinia powyższa dotyczy: projektu badawczego będącego podstawą rozprawy doktorskiej

Wrocław, dnia 28 czerwca 2018 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel

BW