Evidenzreport Triple-Therapie nach akutem koronarem Syndrom bei gleichzeitiger Notwendigkeit einer Antikoagulations-Behandlung

Fragestellung:

Hat eine Triple-Therapie nach akutem koronarem Syndrom bei gleichzeitiger Notwendigkeit einer Antikoagulations-Behandlung Vorteile? Kann ggfs. im Sinne der Senkung der Blutungsrate auf eine der drei Substanzen verzichtet werden?

Systematische Literaturrecherche:

Recherche nach Studien in MEDLINE am 24.5.2013 und in der Cochrane Database of systematic reviews am 1.7.2013. Nachrecherchen am 2.10.2013 sowie am 6.2.2015 ergaben keine neuen Treffer. Aktualisierungs-Recherche in Medline am 15.1.2018 mit Recherche-Zeitraum 6.2.2015-15.1.2018, in Cochrane am 2.11.2018 ohne Begrenzung des Recherche-Zeitraumes.

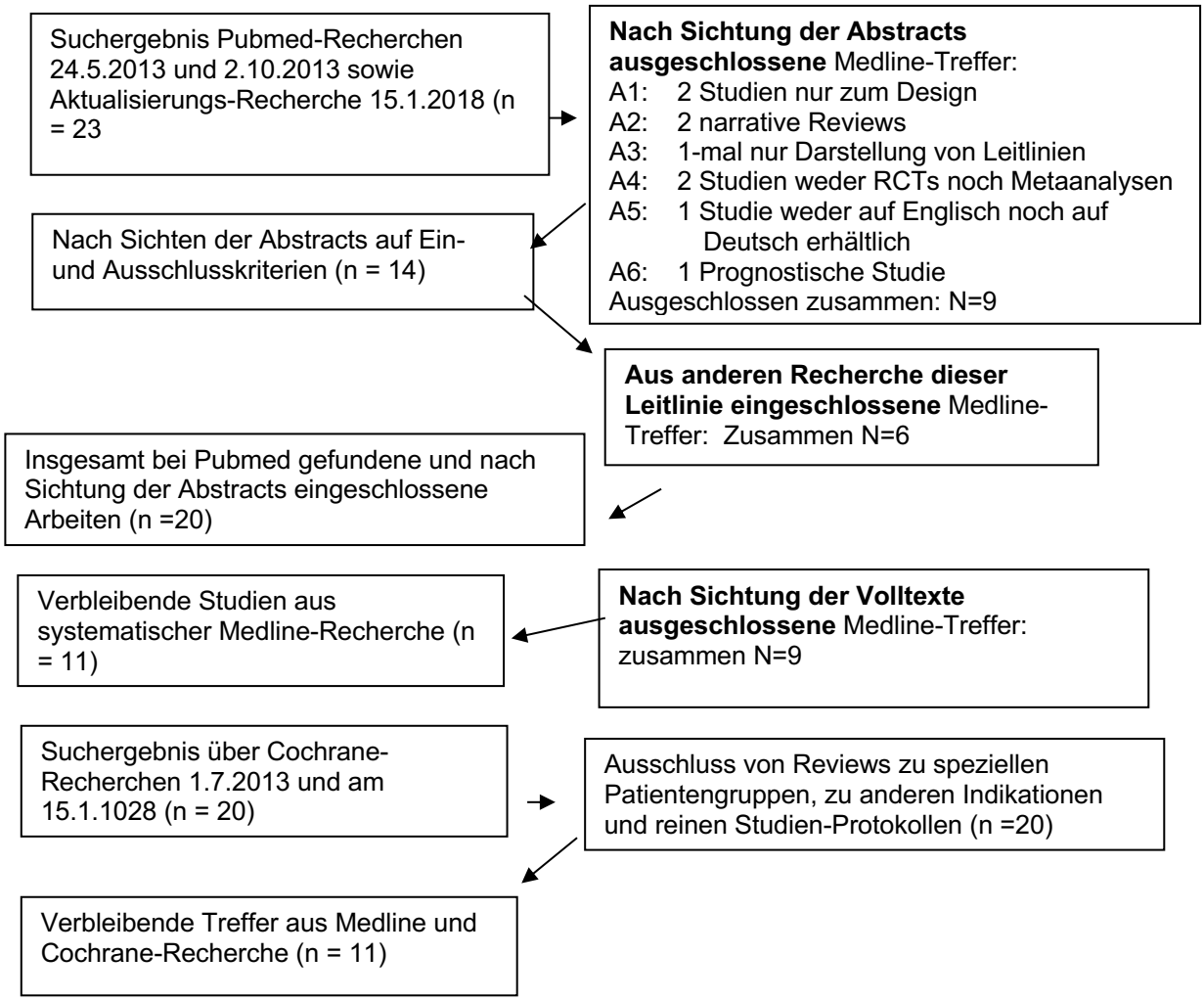
Suchworte: Triple-therapy UND stents ODER coronary stent ODER drug-eluting stent ODER bare-metal stent ODER stent thrombosis UND antiplatelet ODER prasugrel ODER ticagrelor ODER clopidogrel ODER thienopyridine UND warfarin ODER phenprocoumon (Limits: RCTs, Metaanalysen und Syst. Reviews, Studien an Menschen, bei der Cochrane-Suche keine limits

Die gefundenen Treffer wurden nach Ein- und Ausschlusskriterien (Tabelle 1) untersucht. Zunächst wurde ein Titel und Abstract-Screening durchgeführt, dann wurden die Volltexte von beiden Leitlinien-Autoren unabhängig voneinander bewertet.
Einen Überblick über die Literaturrecherche gibt die Abbildung.

Tabelle 1: Ein- und Ausschlusskriterien

	Einschlusskriterien (E)
	Population: Personen nach akutem koronarem Syndrom mit der Notwendigkeit einer Antikoagulationsbehandlung
	Intervention: Neue Antikoagulanzien
	Control: Triple-Therapie aus ASS, Thienopyridin und Antikoagulans
	Outcome: kardiovaskuläre Ereignisse und/oder Tod
	Ausschlusskriterien (A): Studien ausschließlich zum Design (A1), narrative Reviews (A2), Darstellung nur von Leitlinien (A3), kein RCT/keine Metaanalyse (A4), Artikel nicht auf Deutsch oder Englisch erhältlich (A5), rein prognostische Studien (A6)

Abbildung: Flowchart Literaturrecherche



Zusammenfassung Rechercheergebnisse:

Die Recherche in Pubmed und in der Cochrane-Datenbank ergab 11 Arbeiten. Insgesamt ist die Datenlage sehr unzureichend – 4 Studien waren reine Kohortenanalysen bzw. Registerstudien. Sämtliche 12 syst. Reviews/Metaanalysen schlossen entweder keine oder nur einen RCT (2) mit ein – entsprechend hoch ist das Risiko für einen systematischen Bias.
Die Studien wurden dennoch im Evidenzreport belassen, weil ihre Ergebnisse mit denen der beiden RCTs (2,5) konkordant sind. Die beiden RCTs schlossen 1187 Patienten ein.
Grundlagen der eingeschlossenen Metaanalysen waren überwiegend nicht randomisierte Studien mit Laufzeit zwischen einem und 18 Monaten. Im Vergleich mit einer dualen Plättchenhemmung (DAPT) allein senkte die zusätzliche Antikoagulation Insult-Risiko und Gesamtsterblichkeit signifikant, allerdings um den Preis einer Verdopplung schwerer Blutungen.
Nur ein RCT (2) verglich die Kombination von Clopidogrel plus Antikoagulation mit einer Triple-Therapie. Die Rate aller Blutungen und auch die Gesamtsterblichkeit lag unter der Triple-Therapie gut doppelt so hoch wie unter Clopidogrel plus Antikoagulation (s.u.). Schwere Blutungen und ischämische Ereignisse traten unter der Triple-Therapie numerisch häufiger auf. Die Ergebnisse dieses RCT wurden allerdings durch eine große Populationsbasierte Kohorte aus Dänemark (3) bekräftigt.
Im zweiten RCT (6) wurde bei 614 Patienten nach koronarer Intervention mit Stent eine 6-wöchige mit einer 6-monatigen Clopidogrel-Behandlung verglichen. Ischämische und Blutungs-Endpunkte unterschieden sich dabei nicht signifikant. Die Übertragbarkeit der Ergebnisse dieser Studie ist dadurch eingeschränkt, dass Clopidogrel und nicht, wie die WOEST-Studie (2) es nahelegen würde, ASS pausiert wurde. Zudem besteht ein Verzerrungs-Risiko durch das offene Studien-Design.
Da die meisten Metaanalysen neben der WOEST-Studie (2) nur – teils retrospektive – Kohorten einbezogen, sind grundsätzliche Aussagen aus diesen Metaanalysen nur schwer zu generieren.
Nach der derzeitigen Datenlage erscheint es gerechtfertigt, bei antikoagulierten Patienten mit Notwendigkeit einer PTCA die Dauer einer Triple-Therapie nach der PTCA möglichst kurz zu halten und früh auf eine Kombination Antikoagulation plus Clopidogrel umzusetzen.

Zusammenfassung:
Wenn antikoagulierte Patienten sich einer koronaren Katheter-Intervention unterziehen müssen, sollte nach einer möglichst kurzen Phase einer Triple-Therapie (nach unbeschichtetem Stent 4 Wochen, nach beschichtetem Stent 3 Monate) im Sinn einer Minimierung des Blutungsrisikos nur mit Clopidogrel und Phenprocoumon bzw. Warfarin behandelt werden. Die Ziel-INR sollte bei Patienten mit Vorhofflimmern, Thrombophilie und Aorten-Kunstklappe nur bei 2,0-2,5 liegen.

Im Frühjahr 2021 entschlossen sich die Leitlinien-Autoren, die folgenden beiden, zum Zeitpunkt der systematischen Evidenz-Recherche noch nicht vorliegenden Studien zur Dauer einer Thrombozyten-Aggregationshemmung bei antikoagulierten Patienten mit zu berücksichtigen:
Costa F, van Klaveren D, James S et al for the PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-

DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025-1034

Palmerini T, Della Riva D, Benedetto U et al. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. Eur Heart J 2017;38:1034-1043

In Kenntnis der Ergebnisse dieser Studien sowie der Evidenz für das potenzielle Blutungsrisiko bei kombinierter Thrombozytenaggregationshemmung und Antikoagulation resultierte die Modifikation der Empfehlungen zu

- stabiler KHK – Verkürzung der Gabe von Clopidogrel auf 6 Monate bei hohem und auf 1-3 Monate bei sehr hohem Blutungsrisiko und
- akutem Koronarsyndrom – Verkürzung der Gabe von ASS auf 4 Wochen sowie von Clopidogrel auf 6 Monate in Situation mit deutlich erhöhtem Blutungsrisiko.

Anhang: Evidenztabelle

Tabelle 2: RCTs, Metaanalysen und/oder systematische Reviews zum Thema Prasugrel vs. Clopidogrel beim akuten koronaren Syndrom

(Die Ziffer oben in der linken Spalte verweist auf die Reihenfolge der Treffer in der Pubmed-Recherche. Treffer aus der Nachrecherche am 15.1.2018 werden mit dem Buchstaben b) versehen dargestellt

Autor; Jahr	Studientyp, Studienkollektiv	Outcome	Bewertung der Studie
Hansen ([1]) 2010, Dänemark	Populationsbasierte Kohortenstudie aller 82.854 dänischen Patienten, die zwischen 1.1.1997 und 31.12.2006 eine erste stationäre Behandlung wegen Vorhofflimmerns überlebt hatten und Warfarin, ASS, Clopidogrel bzw. Kombinationen davon einnahmen. Diese Studie wurde im Evidenzreport belassen, weil sie aus einem nationalen Register stammt. Das Bias-Risiko ist hier geringer als bei einer einfachen Kohorten-Betrachtung.	Assoziation der Gerinnungs-hemmenden Medikation mit unterschiedlich schweren Blutungen	Nach durchschnittlich 3,3 Jahren erlitten 13.573 Patienten (11,4%) eine schwerere Blutung. Inzidenz unter Clopidogrel+ASS 13,9% und unter Triple-Therapie 15,7 % pro Patienten-Jahr. Verglichen mit Warfarin lag die HR für ASS allein bei 0,93 (95% CI 0,88-0,98), für Clopidogrel bei 1,06 (95% CI 0,87-1,26), für ASS+Clopidogrel bei 1,66 (95% CI 1,34-2,04), für Warfarin+ASS bei 1,83 (95% CI 1,72-1,96), für Warfarin+Clopidogrel bei 3,08 (95% CI 2,32-3,91) und für die Triple-Therapie bei 3,70 (95% CI 2,89-4,76). Die Untersuchung zeigt, dass in der Versorgungssituation das Risiko von Blutungen unter der Kombination von Antikoagulation mit Plättchenhemmern relevant ansteigt. Sie lässt aber letztlich keine exakte Quantifizierung der Risiken zu, da Verzerrungen der Ergebnisse durch differierende Blutungs-Grundrisiken der Patienten durch Adjustierungen nicht vollständig eliminiert werden können.

Autor; Jahr	Studientyp, Studienkollektiv	Outcome	Bewertung der Studie
De Wilde ([2]) 2013 Niederlande und Belgien	RCT, 573 Patienten mit PTCA (28% ACS; 65% DES) unter Antikoagulation erhielten nur Clopidogrel+ Antikoagulation oder eine Triple-Therapie	Primärer Endpunkt: alle Blutungen nach 12 Monaten. Sekundäre Endpunkte: Tod, schwere Blutungen und ischämische Ereignisse.	Unter Clopidogrel+ Antikoagulation kam es bei 19,4% zu Blutungen im Vergleich zu 44,4% unter Triple-Therapie (HR 0,36, 95%-CI 0,26-0,50, p=0,0001). Größere Blutungen traten numerisch seltener auf (HR 0,56, 95%-CI 0,25-1,27; p=0,159). In der Clopidogrel-+Antikoagulationsgruppe lagen Gesamtsterblichkeit signifikant (HR 0,39, 95%-CI 0,16-0,93, p=0,027), Infarkt- und Insultrate nicht signifikant niedriger. Die zumindest tendenziell unter der Zweifachtherapie niedrigeren ischämischen Ereignisse überraschen. Allerdings wurde die Arbeit nicht für solche Endpunkte gepowert. Problematisch erscheint zudem, dass größere Blutungen nicht als primärer Endpunkt definiert waren.
Lamberts ([3]) 2013 Dänemark	Bevölkerungsbasierte Kohorte; das Risiko von 12.165 Patienten mit Vorhofflimmern und Infarkt und/oder PTCA wurde berechnet. Auch diese populationsbasierte Kohorte wurde im Report belassen, weil die Datenbasis zuverlässiger als bei einer einfachen Kohortenanalyse erscheint.	Infarkt, kardiovaskulärer Tod, Insult und Blutungen	Nach einem Jahr kam es unter Warfarin+Clopidogrel (HR 0,69, 95% CI 0,48-1,00), unter Warfarin+ASS(HR 0,96, 95% CI 0,77-1,19) und unter ASS+Clopidogrel (HR 1,17, 95%CI 0,96-1,42) nicht häufiger zu Reinfarkten als unter einer Triple-Therapie. Unter ASS+Clopidogrel kam es häufiger zu Insulten (HR 1,50;95% CI 1,03-2,20). Warfarin+ASS und ASS+Clopidogrel waren mit einer höheren Gesamt-sterblichkeit assoziiert (HR 1,52; 95% CI1,17-1,99 bzw. HR 1,60; 95% CI 1,25-2,05). Verglichen mit einer Triple-Therapie war das Blutungsrisiko nicht signifikant niedriger unter Warfarin+Clopidogrel(HR 0,78; 95% CI 0,55-1,12) und signifikant niedriger unter Warfarin+ASS (HR 0,69; 95%-CI 0,53-0,90) bzw. unter ASS+Clopidogrel (HR 0,48; 95%-CI 0,38-0,61)

Autor; Jahr	Studientyp, Studienkollektiv	Outcome	Bewertung der Studie
Lamberts ([4]) 2014 Dänemark	Register-Studie: 8.700 Patienten mit Vorhofflimmern und stabiler KHK zwischen 2002 und 2011 wurden untersucht	diovaskuläre und ernsthafte Blutungen	Vergleich zu Warfarin-Monotherapie lag das Risiko für Infarkte oder Herztod unter Hinzufügung von ASS (HR 1,12; CI 0,94-1,34) bzw. Clopidogrel (HR 1,53; CI 0,93-2,52) etwa gleich, ebenso das Risiko embolischer Ereignisse. Das Blutungsrisiko dagegen stieg mit Hinzufügung von ASS (HR 1,5; 95% CI 1,32-1,82) wie von Clopidogrel (HR 1,84; 95% CI 1,11-3,06) dagegen deutlich.
Hess ([5]) 2018	Registerstudie zu 4.959 US-amerikanischen Medicare-Patienten mit Vorhofflimmern, die nach Infarkt eine Triple-Therapie erhielten	Größere kardiovaskuläre Ereignisse (MACE), Insulte, Gesamtsterblich-keit, größere Blutungen	MACE waren vergleichbar häufig wie unter einer dualen Therapie (HR 0,99, CI 0,86-1,16), aber ein größeres Risiko größerer zur Klinikaufnahme führender Blutungen (HR 1,61, CI 1,31-1,97).
Aus anderer Recherche Fiedler ([6]) 2015	Offener RCT mit 614 antikoagulierten Patienten an 3 europäischen Zentren, die nach PCI TAH erhielten. Dabei wurde eine 6-wöchige Clopidogrel-Gabe mit einer 6-monatigen verglichen	Primärer Sammel-Endpunkt aus Tod, Infarkt, Stent-Thrombose, Insult, größere Blutungen	Der primäre Sammelendpunkt ereignete sich numerisch etwas häufiger unter der kurzen vs. der längeren Triple-Therapie (9,8 vs. 8,8%, HR 1,14, CI 0,68-1,91, p=0,63). Die einzelnen Bestandteile des Sammel-endpunktes unterschieden sich nicht signifikant, ebenso wenig die größeren Blutungen. Problem ist bei dieser Studie neben dem offenen Design, dass bei der Hälfte der Patienten Clopidogrel und nicht ASS vorzeitig pausiert wurde. Über den Ausgang einer möglichen Kombination OAK+Clopi mit und ohne ASS können hiermit keine Aussagen getroffen werden.

Autor; Jahr	Studientyp, Studienkollektiv	Outcome	Bewertung der Studie
Aus anderer Recherche Gao ([7]) 2015	Metaanalyse aus 16 Studien mit 9.185 antikoagulierten Patienten, die bei einem Stent eine Triple-Therapie oder eine duale Behandlung mit Clopi+OAK oder DAPT bekamen	Größere kardiovaskuläre Ereignisse, Gesamt-sterblichkeit, Infarkt, Stent-Thrombose, Insult und Größere Blutungen	Größere kardiovaskuläre Ereignisse (OR 1,06, CI 0,81-1,39, p=0,65), Gesamt-sterblichkeit (OR0,98, CI 0,76-1,27, p=0,89), Infarkte (OR 1,01, CI 0,77-1,31, p=0,97) und Stent-Thrombosen (OR OR 0,91, CI 0,49-1,69, p=0,75) waren ähnlich zwischen Triple- und dualer Therapie. Eine Triple-Therapie ging mit weniger Insulten (OR 0,57, CI 0,35-0,94, p=0,03), aber mehr größeren Blutungen (OR 1,52, CI 1,11-2,10, p=0,01) einher. Eine Subgruppen-Analyse zeigte ein vergleichbares Ergebnis im Vergleich zwischen Triple und OAK+Clopi auch hinsichtlich Insult und größeren Blutungen. Die Aussagekraft der Metaanalyse ist eingeschränkt dadurch, dass neben einem RCT nur – größeren Teils retrospektive - Kohorten mit hohem Verzerrungs-Risiko eingeschlossen wurden.
Golwala ([8]) 2018	Metaanalyse zu 4 RCTs mit 5.317 Patienten mit Vorhofflimmern, die nach PCI eine Triple- vs. eine duale Therapie erhielten	Größere Blutungen, größere kardiale Ereignisse	Unter einer dualen Therapie gab es deutlich weniger größere Blutungen (4,3 vs. 9,0%, HR 0,53, CI 0,36-0,85), aber nicht mehr größere kardiale Ereignisse (10,4 vs. 10,0%, HR 0,85, CI 0,48-1,29). Problem bei dieser Metaanalyse ist die Berücksichtigung der NOAK-Studien PIONEER-AF-PCI und RE-DUAL PCI – deren Limitationen wurden im Evidenzreport zu Triple-Therapie mit NOAK erörtert.

Autor; Jahr	Studientyp, Studienkollektiv	Outcome	Bewertung der Studie
Aus anderer Recherche Jackson ([9]) 2015	Nachanalyse der TRANSLATE-ACS-Studie mit 11.756 Infarkt-Patienten, die eine Triple-Therapie mit Clopi (526 Pat), Prasugrel (91 Pat) oder eine DAPT mit Clopi (7.715 Pat) oder Prasugrel (3.424 Pat) erhielten. Es wurde ein Propensity-Score-Matching durchgeführt.	Größere Blutungen	Eine Triple-Therapie mit Clopi führte zu mehr größeren Blutungen als eine DAPT mit Clopi (28,7 vs. 19,7%, RR 1,68, CI 1,29-2,81, p=0,0001), ebenso eine Triple mit Prasu vs. DAPT mit Prasu (38,5 vs. 26,7%, RR 1,88, CI 1,10-3,20, p=0,02) und auch eine Triple mit Prasu vs. Triple mit Clopi (39,0 vs. 24,4%, RR 2,37, CI 1,36-4,15, p=0,003). Die Aussagekraft dieser Studie ist dadurch eingeschränkt, dass es sich nicht um einen RCT, sondern eine gematchte Nachanalyse handelte. Die Studie gibt aber einen Hinweis darauf, dass, was wir bereits aus der Prasugrel-Zulassungsstudie TRITON-TIMI 38 wissen, Prasugrel eher mit mehr größeren Blutungen einher geht als Clopidogrel
Khan ([10]) 2018	Metaanalyse zu 9 Studien (4 RCTs und 5 Kohorten) mit 13.704 Patienten (in RCTs 6.790 Patienten) mit Vorhofflimmern, die eine Triple-Therapie oder OAK mit einem TAH erhielten	Größere Blutungen, größere kardiovaskuläre Ereignisse, Infarkte	In den RCTs führte die Kombination OAK+einem TAH zu weniger Blutungen (RR 0,70, CI 0,60-0,81, p<0,001) und ähnlich vielen kardiovaskulären Ereignissen (RR 0,93, CI 0,68-1,27, p=0,64) und Infarkten (RR 1,18, CI 0,89-1,56, p=0,24). Die Kohortenstudien zeigten ähnlich viele Blutungen in beiden Gruppen, aber mehr Infarkte unter OAK+einem TAH. Die Aussagekraft dieser Metaanalyse ist durch die Limitationen der eingeschlossenen RCTS PIONEER AF PCI und RE-DUAL PCI eingeschränkt – zudem durch die methodischen Grenzen von Beobachtungsstudien. Es wurden allerdings RCTs und Beobachtungsstudien separat ausgewertet.

Autor; Jahr	Studientyp, Studienkollektiv	Outcome	Bewertung der Studie
Aus anderer Recherche Liu ([11]) 2016	Metaanalyse zu 18 Studien (1 RCT und 17 Kohorten) mit 17.708 antikoagulierten Patienten, die eine Triple- mit verschiedenen dualen Therapien verglichen hatten	Größere kardiovaskuläre Ereignisse, Insulte, Infarkte, größere Blutungen	OAK + ASS (OR 1,95, CI 1,14-3,33) und DAPT (OR 1,43, CI 1,03-1,99) gingen mit deutlich mehr MACE einher als eine Triple-Therapie. Im direkten Vergleich OAK+ASS mit einer DAPT war erstere numerisch unterlegen (OR 1,16, CI 0,98-1,65), während OAK+Clopi numerisch überlegen war (OR 0,57, CI 0,10-1,04). OAK + ASS (OR 2,61, CI 1,39-4,89) und DAPT (OR 2,35, CI 1,31-4,20) waren mit mehr Insulten als OAK + Clopi oder Triple-Therapie assoziiert. Infarkte traten unter OAK+ASS häufiger auf als unter OAK+Clopi (OR 2,16, CI 1,29-3,60), während das Ergebnis unter Triple-Therapie und OAK und Clopi ähnlich war (OR 1,03, CI 0,76-1,41). OAK+Clopi (OR 2,42, CI 1,73-3,39), +ASS (OR 2,42, CI 1,68-3,50) und DAPT waren mit höherer Gesamtsterblichkeit assoziiert als Triple-Therapie. Hinsichtlich größerer Blutungen waren die Ergebnisse nicht signifikant unterschiedlich. Die Aussagekraft auch dieser Metaanalyse ist eingeschränkt dadurch, dass neben einem RCT nur – größeren Teils retrospektive - Kohorten mit hohem Verzerrungs-Risiko eingeschlossen wurden.

Cochrane-Suche Triple-Therapie

Cochrane-Suche mit dem Suchbegriff „Triple therapy “ am 2.11.2018

Alle gefundenen 20 Studien behandelten komplett andere Interventionen, kein einziger Review konnte in den Evidenzreport eingeschlossen werden.
Auch eine erneute Suche mit den Begriffen „oral anticoagulants“ OR „oral anticoagulation“ AND „platetelet inhibition“ OR „dual antiplatelet therapy“ brachte kein Ergebnis

Nr.	Arbeit	Ein-schluss	Begründung
1	Sequential versus standard triple first-line therapy for *Helicobacter pylori* eradication Olga P Nyssen, Adrian G McNicholl, Francis Megraud, Vincenzo Savarino, Giuseppina Oderda, Carlo A Fallone, Lori Fischbach, Franco Bazzoli, Javier P Gisbert Intervention Review 28 June 2016	Nein	Andere Intervention
2	Abacavir-based triple nucleoside regimens for maintenance therapy in patients with HIV Mario Cruciani, Carlo Mengoli, Giovanni Serpelloni, Saverio G Parisi, Marina Malena, Oliviero Bosco Intervention Review 5 June 2013	Nein	Andere Intervention
	Nein	Nein	Andere Intervention
4	Interventions for melasma Ratna Rajaratnam, James Halpern, Asad Salim, Charis Emmett Intervention Review 7 July 2010	Nein	Andere Intervention
5	Platinum-containing regimens for metastatic breast cancer Sam J Egger, Melina L Willson, Jenna Morgan, Harriet S Walker, Sue Carrick, Davina Ghersi, Nicholas Wilcken Intervention Review 23 June 2017	Nein	Andere Intervention
6	Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection Nandi Siegfried, Lize van der Merwe, Peter Brocklehurst, Tin Tin Sint Intervention Review 6 July 2011	Nein	Andere Intervention
7	Sildenafil citrate for erectile dysfunction in patients with multiple sclerosis Yousheng Xiao, Jin Wang, Hongye Luo Intervention Review 18 April 2012	Nein	Andere Intervention
8	Pegylated liposomal doxorubicin for first-line treatment of epithelial ovarian cancer Theresa A Lawrie, Roy Rabbie, Clemens Thoma, Jo Morrison Intervention Review 21 October 2013	Nein	Andere Intervention

9	Co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection and AIDS Muki S Shey, Eugene J Kongnyuy, Samuel M Alobwede, Charles S Wiysonge Intervention Review 28 March 2013	Nein	Andere Intervention
10	Antiretroviral interventions for preventing breast milk transmission of HIV Angela B White, Joy F Mirjahangir, Hacsi Horvath, Andrew Anglemyer, Jennifer S. Read Intervention Review 4 October 2014	Nein	Andere Intervention
11	Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women Amy S Sturt, Emily Kainne Dokubo, Tin Tin Sint Intervention Review 17 March 2010	Nein	Andere Intervention
12	Anticholinergic drugs versus placebo for overactive bladder syndrome in adults Ghulam Nabi, June D Cody, Gaye Ellis, Jean Hay-Smith, G Peter Herbison Intervention Review 18 October 2006	Nein	Andere Intervention
13	Behavioural and cognitive-behavioural group-based parenting programmes for early-onset conduct problems in children aged 3 to 12 years Mairead Furlong, Sinead McGilloway, Tracey Bywater, Judy Hutchings, Susan M Smith, Michael Donnelly Intervention Review 15 February 2012	Nein	Andere Intervention
14	Splinting for carpal tunnel syndrome Matthew J Page, Nicola Massy-Westropp, Denise O'Connor, Veronica Pitt Intervention Review 11 July 2012	Nein	Andere Intervention
15	Combination inhaled steroid and long-acting $beta_2$-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease Maria Ximena Rojas-Reyes, Olga M García Morales, Rodolfo J Dennis, Charlotta Karner Intervention Review 6 June 2016	Nein	Andere Intervention
16	Interventions for primary vesicoureteric reflux Evi VT Nagler, Gabrielle Williams, Elisabeth M Hodson, Jonathan C Craig Intervention Review 15 June 2011	Nein	Andere Intervention
17	Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) Robert G Miller, J D Mitchell, Dan H Moore Intervention Review 14 March 2012	Nein	Andere Intervention
18	Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults Khin Hnin, Chau Nguyen, Kristin V Carson-Chahhoud, David J Evans, Michael Greenstone, Brian J Smith Intervention Review 13 August 2015	Nein	Andere Intervention

19	The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women Oyinlola O Oduyebo, Rose I Anorlu, Folasade T Ogunsola Intervention Review 8 July 2009	Nein	Andere Intervention
20	Knee orthoses for treating patellofemoral pain syndrome Toby O Smith, Benjamin T Drew, Toby H Meek, Allan B Clark Intervention Review 8 December 2015	Nein	Andere Intervention
21	Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients Penny Hill, Nicholas B Cross, A Nicholas R Barnett, Suetonia C Palmer, Angela C Webster Intervention Review 11 January 2017	Nein	Andere Intervention
22	Adjuvant chemotherapy for advanced endometrial cancer Khadra Galaal, Mansour Al Moundhri, Andrew Bryant, Alberto D Lopes, Theresa A Lawrie Intervention Review 15 May 2014 Free access	Nein	Andere Intervention
23	Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis Glen S Hazlewood, Cheryl Barnabe, George Tomlinson, Deborah Marshall, Daniel JA Devoe, Claire Bombardier Overview Review 29 August 2016	Nein	Andere Intervention
24	Antibiotic regimens for management of intra-amniotic infection Evelina Chapman, Ludovic Reveiz, Eduardo Illanes, Xavier Bonfill Cosp Intervention Review 19 December 2014	Nein	Andere Intervention
25	Operative caries management in adults and children David Ricketts, Thomas Lamont, Nicola PT Innes, Edwina Kidd, Jan E Clarkson Intervention Review 28 March 2013	Nein	Andere Intervention
26	*Serenoa repens* for benign prostatic hyperplasia James Tacklind, Roderick MacDonald, Indy Rutks, Judith U Stanke, Timothy J Wilt Intervention Review 12 December 2012	Nein	Andere Intervention
27	Topical phenytoin for treating pressure ulcers Xiang Yong Hao, Hong Ling Li, He Su, Hui Cai, Tian Kang Guo, Ruifeng Liu, Lei Jiang, Yan Fei Shen Intervention Review 22 February 2017	Nein	Andere Intervention
28	Bisphosphonates for Paget's disease of bone in adults Luis Corral-Gudino, Adrian JH Tan, Javier del Pino-Montes, Stuart H Ralston Intervention Review 1 December 2017	Nein	Andere Intervention

29	Bile acids for liver-transplanted patients Goran Poropat, Vanja Giljaca, Davor Stimac, Christian Gluud Intervention Review 17 March 2010	Nein	Andere Intervention

Pubmed-Suche Triple-Therapie

Es wurden 4 Pubmed-Suchen durchgeführt am 24.5.2013, am 2.10.2013, am 6.2.2015 und in einer Aktualisierungs-Recherche am 15.1.2018

Ein- und Ausschluss der gefundenen insgesamt 14 Studien:

Ausschluss:	
Darstellung nur von Leitlinien	2
Studien nur zum Design	2
Narrative Reviews	2
Keine Original-Arbeiten	2
Abstract nicht auf Englisch/Deutsch verfügbar	1
Eingeschlossene Studien	5
	14

Aktualisierungs-Recherche am 15.1.2018

Ein- und Ausschluss der gefundenen 6 Studien:

Ausschluss:	
Studien ausschließlich zum Design	2
Narrative Reviews	2
Eingeschlossene Studien (in der Tabelle gelb, markiert)	2
	6

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#17	Add	Search **((((triple therapy AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) AND (((((((stents AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (coronary stent AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (**	6	03:21:03

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		German[lang] OR English[lang])))) OR (bare-metal stent AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (drug-eluting stent AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (stent thrombosis AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) AND (((((((antiplatelet AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (prasugrel AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (ticagrelor AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (clopidogrel AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (thienopyridine AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) AND ((((warfarin AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND (			

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#16	Add	Search **((warfarin AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))) OR (phenprocoumon AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang])))** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	394	03:19:46
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		OR Meta-Analysis[ptyp]) AND ("2015/02/05"[PDat] : "2018/01/15"[PDat]) AND Humans[Mesh] AND (German[lang] OR English[lang]))) Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**		
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#12	Add	Search **warfarin** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	391	03:17:40
#11	Add	Search **thienopyridine** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	42	03:17:31
#10	Add	Search **clopidogrel** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis;**	397	03:17:25

Recent queries

Search	Add to builder	Query	Items found	Time
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#9	Add	Search **ticagrelor** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	165	03:17:18
#8	Add	Search **prasugrel** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	134	03:17:12
#7	Add	Search **antiplatelet** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	607	03:17:07
#6	Add	Search **stent thrombosis** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	432	03:16:52
#5	Add	Search **bare-metal stent** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	105	03:16:44
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#3	Add	Search **coronary stent** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	809	03:16:30
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#1	Add	Search **triple therapy** Filters: **Systematic Reviews; Randomized Controlled Trial; Meta-Analysis; Publication date from 2015/02/05 to 2018/01/15; Humans; German; English**	572	03:16:12

Nr.	Arbeit	Ein-schluss	Begründung
1b)	Clin Cardiol. Cannon Design and Rationale of the RE-DUAL PCI Trial: A Prospective, Randomized, Phase 3b Study Comparing the Safety and Efficacy of Dual Antithrombotic Therapy With Dabigatran Etexilate Versus Warfarin Triple Therapy in Patients	Nein	A1

	With Nonvalvular Atrial Fibrillation Who Have Undergone Percutaneous Coronary Intervention With Stenting. DOI: 10.1002/clc.22572		
2b)	Cardiovasc Drugs Ther. Barbieri Risk and Benefits of Triple Therapy in Patients Undergoing Coronary Stent Implantation Requiring Oral Anticoagulation: A Meta-Analysis of 16 Studies. DOI: 10.1007/s10557-016-6692-z	Ja	
3c)	Catheter Cardiovasc Interv. Bavishi Evaluation of the efficacy and safety of dual antiplatelet therapy with or without warfarin in patients with a clinical indication for DAPT and chronic anticoagulation: A meta-analysis of observational studies. Bavishi C[1], Koulova A[1], Bangalore S DOI: 10.1002/ccd.26234	ja	
4	J Thromb Haemost. Verheugt Triple therapy for percutaneous coronary intervention in atrial fibrillation: standard of care, or a nightmare soon to end? DOI: 10.1111/jth.12936	Nein	A2
5	Contemp Clin Trials. Gao Rationale and design of the RT-AF study: Combination of rivaroxaban and ticagrelor in patients with atrial fibrillation and coronary artery disease undergoing percutaneous coronary intervention. DOI: 10.1016/j.cct.2015.05.012	Nein	A1
6	Hamostaseologie. Lüscher Individualized antithrombotic therapy. DOI: 10.5482/HAMO-14-12-0080	Nein	A2

Zusätzlich Treffer zum Thema bei Durchführung von Recherchen zu anderen Fragen:

29	Int J Clin Pharmacol Ther. 2016 Dec;54(12):950-965. **Short- and long-term efficacy and safety of triple vs. dual antithrombotic therapy in patients with drug-eluting stent implantation and an indication for oral anticoagulation: a meta-analysis.** Cao Y, Tian XY, Zhang R, Zhao JQ, Zhang M, Cheng YT, Li CF, Liu GL, An Y. **Abstract** **BACKGROUND:** The optimal antithrombotic regimen after coronary stenting in patients taking oral anticoagulants (OACs) is still unclear. Therefore, this meta-analysis focused on the short- and long-term efficacy and safety of triple therapy (TT: OAC, aspirin, and thienopyridine) and dual therapy (DT: OAC plus single antiplatelet drug or aspirin plus thienopyridine). **METHODS:** We searched PubMed, Embase, the Cochrane Library, Wangfang database, and Google Scholar up to December 1, 2015 (January 1, 2000 - December 2015), from randomized and nonrandomized studies comparing TT and DT in patients with OACs undergoing drug-eluting stent (DES) implantation. Major adverse cardiac and

	cerebrovascular events (MACCE) were the main outcome. Safety outcome was major bleeding (MB). **RESULTS:** Of 964 publications identified, 1 randomized study and 27 nonrandomized studies of 31,346 patients were included. Overall, TT and OAC plus clopidogrel were associated with a lower risk of MACCE, stroke, MI, and allcause mortality compared with dual antiplatelet therapy or OAC plus aspirin. Additionally, short-term use of triple antithrombotic regimen with OAC, aspirin, and clopidogrel is associated with equivalent risk of major bleeding and decreased rate of MACCE. Long-term use of OAC plus clopidogrel after TT was associated with equal or better benefit and safety outcomes. **CONCLUSION:** For patients on OAC after coronary stenting, triple therapy (OAC, aspirin, clopidogrel) should be considered in the short term, followed by more long-term therapy with OAC plus clopidogrel. More randomized studies are needed to confirm these findings. PMID: 27641219 DOI: 10.5414/CP202653 [Indexed for MEDLINE]
88	J Am Coll Cardiol. 2015 Apr 28;65(16):1619-1629. doi: 10.1016/j.jacc.2015.02.050. **Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation: The ISAR-TRIPLE Trial.** Fiedler KA[1], Maeng M[2], Mehilli J[3], Schulz-Schüpke S[1], Byrne RA[4], Sibbing D[3], Hoppmann P[5], Schneider S[5], Fusaro M[1], Ott I[1], Kristensen SD[2], Ibrahim T[5], Massberg S[3], Schunkert H[4], Laugwitz KL[6], Kastrati A[4], Sarafoff N[7]. **Author information** **Abstract** **BACKGROUND:** Patients receiving oral anticoagulation (OAC) who undergo drug-eluting stent (DES) implantation require additional dual antiplatelet therapy with aspirin and clopidogrel. Such triple therapy confers an elevated bleeding risk, and its optimal duration is not known. **OBJECTIVES:** The goal of this study was to evaluate whether shortening the duration of clopidogrel therapy from 6 months to 6 weeks after DES implantation was associated with a superior net clinical outcome in patients receiving concomitant aspirin and OAC. **METHODS:** In this randomized, open-label trial, we enrolled patients receiving OAC who underwent DES implantation at 3 European centers between September 2008 and December

	2013. A total of 614 patients receiving concomitant aspirin and OAC were randomized to either 6-week clopidogrel therapy (n=307) or 6-month clopidogrel therapy (n=307). The primary endpoint was a composite of death, myocardial infarction (MI), definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months. **RESULTS:** The primary endpoint occurred in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (hazard ratio [HR]: 1.14; 95% CI: 0.68 to 1.91; p=0.63). There were no significant differences for the secondary combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, and ischemic stroke (12 [4.0%] vs. 13 [4.3%]; HR: 0.93; 95% CI: 0.43 to 2.05; p=0.87) or the secondary bleeding endpoint of TIMI major bleeding (16 [5.3%] vs. 12 [4.0%]; HR: 1.35; 95% CI: 0.64 to 2.84; p=0.44). **CONCLUSIONS:** Six weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes. These results suggest that physicians should weigh the trade-off between ischemic and bleeding risk when choosing the shorter or longer duration of triple therapy. (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation [ISAR-TRIPLE]; NCT00776633). **KEYWORDS:** aspirin; atrial fibrillation; clopidogrel; percutaneous coronary intervention; vitamin K antagonist **Comment in** • Reply: Duration of Triple Therapy: A Clinical Question Yet to Be Answered. [J Am Coll Cardiol. 2015] • When Is a Double Better Than a TRIPLE?: Stenting in Patients With Atrial Fibrillation. [J Am Coll Cardiol. 2015] • Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation. [J Am Coll Cardiol. 2015] • Reply: Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation. [J Am Coll Cardiol. 2015] • Duration of Triple Therapy: A Clinical Question Yet to Be Answered. [J Am Coll Cardiol. 2015] PMID: 25908066 DOI: 10.1016/j.jacc.2015.02.050 [Indexed for MEDLINE] Free full text
140	J Am Coll Cardiol. 2015 Apr 28;65(16):1619-1629. doi: 10.1016/j.jacc.2015.02.050.

Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation: The ISAR-TRIPLE Trial.

Fiedler KA[1], Maeng M[2], Mehilli J[3], Schulz-Schüpke S[1], Byrne RA[4], Sibbing D[3], Hoppmann P[5], Schneider S[5], Fusaro M[1], Ott I[1], Kristensen SD[2], Ibrahim T[5], Massberg S[3], Schunkert H[4], Laugwitz KL[6], Kastrati A[4], Sarafoff N[7].

Author information

Abstract

BACKGROUND:

Patients receiving oral anticoagulation (OAC) who undergo drug-eluting stent (DES) implantation require additional dual antiplatelet therapy with aspirin and clopidogrel. Such triple therapy confers an elevated bleeding risk, and its optimal duration is not known.

OBJECTIVES:

The goal of this study was to evaluate whether shortening the duration of clopidogrel therapy from 6 months to 6 weeks after DES implantation was associated with a superior net clinical outcome in patients receiving concomitant aspirin and OAC.

METHODS:

In this randomized, open-label trial, we enrolled patients receiving OAC who underwent DES implantation at 3 European centers between September 2008 and December 2013. A total of 614 patients receiving concomitant aspirin and OAC were randomized to either 6-week clopidogrel therapy (n=307) or 6-month clopidogrel therapy (n=307). The primary endpoint was a composite of death, myocardial infarction (MI), definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months.

RESULTS:

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

CONCLUSIONS:

Six weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes. These results suggest that physicians should weigh the trade-off between ischemic and bleeding risk when choosing the shorter or longer duration of triple therapy. (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation [ISAR-TRIPLE]; NCT00776633).

KEYWORDS:

	aspirin; atrial fibrillation; clopidogrel; percutaneous coronary intervention; vitamin K antagonist Comment in • Reply: Duration of Triple Therapy: A Clinical Question Yet to Be Answered. [J Am Coll Cardiol. 2015] • When Is a Double Better Than a TRIPLE?: Stenting in Patients With Atrial Fibrillation. [J Am Coll Cardiol. 2015] • Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation. [J Am Coll Cardiol. 2015] • Reply: Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation. [J Am Coll Cardiol. 2015] • Duration of Triple Therapy: A Clinical Question Yet to Be Answered. [J Am Coll Cardiol. 2015] PMID: 25908066 DOI: 10.1016/j.jacc.2015.02.050 [Indexed for MEDLINE] Free full text
122	Herz. 2015 Dec;40(8):1070-83. doi: 10.1007/s00059-015-4325-0. Epub 2015 Jul 2. **Antithrombotic therapy after percutaneous coronary intervention in patients requiring oral anticoagulant treatment. A meta-analysis.** Chen CF[1], Chen B[1], Zhu J[1], Xu YZ[2]. Author information Abstract *AIM:* The aim of this meta-analysis was to evaluate the benefits and risks of triple therapy (TT) compared with dual therapy (DT) for patients with an indication for anticoagulation who had undergone percutaneous coronary intervention. *BACKGROUND:* An increasing number of patients undergoing percutaneous coronary intervention have atrial fibrillation or other indications for oral anticoagulants. For these patients, TT (oral anticoagulants plus aspirin and clopidogrel) is indicated, but this type of treatment increases the risk of bleeding. Thus, it remains controversial whether these patients can benefit more from TT. *METHODS:* We identified 23 clinical trials that compared TT with DT (aspirin and clopidogrel or oral anticoagulants plus a single antiplatelet drug) after percutaneous coronary intervention in patients undergoing oral anticoagulant (OAC) treatment. The follow-up period ranged from 1 month to 25 months. Two coauthors independently recorded the data on interventions and on the occurrence of major adverse cardiac events (MACE), all-cause death, and major bleeding events.

	RESULTS: The 23 clinical trials comprised 22,212 participants. Our analysis was feasible because the baseline characteristics and grouping criteria were similar in all groups. The results indicated that TT was more efficacious than DT [dual antiplatelet (DAPT) or OAC + single antiplatelet] in reducing MACE/stroke (RR = 0.76, 95 % CI: 0.70-0.83; p < 0.00001 and RR = 0.67, 95 % CI: 0.59-0.75; p < 0.00001, respectively) There was a significant reduction in all-cause death in the TT regimen compared with the DT regimen (RR = 0.64, 95 % CI: 0.56-0.73; p < 0.00001 and RR = 0.48, 95 % CI: 0.39-0.58; p < 0.00001, respectively). In a subgroup analysis without retrospective studies, we found that there was no significant difference between TT and DT with regard to MACE/stroke (RR = 1.06, 95 % CI: 0.88-1.27; p = 0.54 and RR = 0.95, 95 % CI: 0.79-1.14; p = 0.58, respectively) and all-cause death (RR = 0.84, 95 % CI: 0.63-1.12; p = 0.24 and RR = 1.13, 95 % CI: 0.78-1.64; p = 0.51, respectively). We also found that TT significantly increased the risk of major bleeding compared with DAPT (RR = 1.36; 95 % CI: 1.17-1.58; p < 0.0001). However, there was no difference between TT and OAC + single antiplatelet agent (RR = 0.96; 95 % CI: 0.75-1.21; p = 0.71). Finally, in the comparison between TT and OAC + clopidogrel, there were no differences in major bleeding events, MACE and stroke, and all-cause death. *CONCLUSION:* Our analysis found no statistically significant difference between TT and DT with regard to all-cause death and MACE/stroke risk. At the same time, the available data demonstrated that TT increased the risk of major bleeding. If the international normalized ratio is in the target range, the risk of bleeding may be lowered. The data from Asian countries were limited, and therefore we could not assess the difference between TT and DT in Asian populations. Finally,on the basis of our analysis, we do not recommend TT as conventional treatment for patients taking OACs and undergoing percutaneous coronary intervention. *KEYWORDS:* Anticoagulant therapy; Antiplatelet treatment; Aspirin; Clopidogrel; Percutaneous coronary intervention PMID: 26135462 DOI: 10.1007/s00059-015-4325-0
135	Clin Cardiol. 2015 Aug;38(8):499-509. doi: 10.1002/clc.22411. Epub 2015 May 12. **Antithrombotic Regimens for Patients Taking Oral Anticoagulation After Coronary Intervention: A Meta-analysis of 16 Clinical Trials and 9,185 Patients.** Gao XF[1,2], Chen Y[3], Fan ZG[1], Jiang XM[1], Wang ZM[1], Li B[1], Mao WX[1], Zhang JJ[1,2], Chen SL[1,2]. Author information Abstract The optimal antithrombotic regimen remains controversial in patients taking oral anticoagulation (OAC) undergoing coronary stenting. This study sought to compare efficacy and safety outcomes of triple therapy (OAC, aspirin, and clopidogrel) vs dual therapy (clopidogrel with aspirin or OAC) in these patients. We hypothesize OAC plus clopidogrel could be the optimal regimen for patients with indications for OAC receiving stent implantation. Medline, the Cochrane Library, and other Internet sources were searched for clinical trials comparing the efficacy and safety of triple vs dual therapy for patients taking OAC after coronary stenting.

	Sixteen eligible trials including 9185 patients were identified. The risks of major adverse cardiac events (odds ratio [OR]: 1.06, 95% confidence interval [CI]: 0.82-1.39, P = 0.65), all-cause mortality (OR: 0.98, 95% CI: 0.76-1.27, P = 0.89), myocardial infarction (OR: 1.01, 95% CI: 0.77-1.31, P = 0.97), and stent thrombosis (OR: 0.91, 95% CI: 0.49-1.69, P = 0.75) were similar between triple and dual therapy. Compared with dual therapy, triple therapy was associated with a reduced risk of ischemic stroke (OR: 0.57, 95% CI: 0.35-0.94, P = 0.03) but with higher major bleeding (OR: 1.52, 95% CI: 1.11-2.10, P = 0.01) and minor bleeding (OR: 1.59, 95% CI: 1.05-2.42, P = 0.03). Subgroup analysis indicated there were similar ischemic stroke and major bleeding outcomes between triple therapy and therapy with OAC plus clopidogrel. Treatment with OAC and clopidogrel was associated with similar efficacy and safety outcomes compared with triple therapy. Triple therapy could be replaced by OAC plus clopidogrel without any concern about additional risk of thrombotic events. Comment in • Duration of Triple Therapy: A Clinical Question Remains Unanswered. [Clin Cardiol. 2015] PMID: 25963316 PMCID: PMC4744725 DOI: 10.1002/clc.22411 [Indexed for MEDLINE] Free PMC Article
88	Int J Cardiol. 2016 Feb 15;205:89-96. doi: 10.1016/j.ijcard.2015.12.005. Epub 2015 Dec 17. **Efficacy and safety of antithrombotic regimens after coronary intervention in patients on oral anticoagulation: Traditional and Bayesian meta-analysis of clinical trials.** Liu J[1], Fan M[2], Zhao J[1], Zhao B[3], Zhang C[1], Liu C[1], Dong Y[4]. Author information Abstract *OBJECTIVE:* To perform a systematic review and meta-analysis to assess the efficacy and safety of diverse antithrombotic regimens in patients on long-term anticoagulation after percutaneous coronary intervention (PCI). *METHODS:* After searching electronic database (up to 27 June 2015), we included trials comparing dual antiplatelet therapy (aspirin plus clopidogrel), oral anticoagulant (OAC) plus clopidogrel, OAC plus aspirin, or triple therapy (OAC with clopidogrel and aspirin). Efficacy outcomes were major adverse cardiovascular event (MACE), ischemic stroke, myocardial infarction (MI), and all-cause mortality; safety outcomes included major bleeding and any bleeding. We conducted both traditional and Bayesian network meta-analysis, computing pooled odds ratio (OR) with 95% confidence intervals (CI) to compare diverse antithrombotic therapies simultaneously.

RESULTS:

Eighteen trials were included in the quantitative analysis. OAC plus clopidogrel and triple therapy were associated with a lower risk of MACE, ischemic stroke, MI and all-cause mortality compared with dual antiplatelet or OAC plus aspirin regimens. OAC plus clopidogrel was ranked the most efficacious option without an increase in bleeding episodes. However, triple therapy improved the efficacy outcomes at the expense of increasing hemorrhage. For the initial short-term outcomes, OAC plus clopidogrel inconclusively reduced the risk of MACE and had a significantly lower risk of any bleeding.

CONCLUSIONS:

OAC plus clopidogrel may be the optimal antithrombotic therapy in patients on oral anticoagulation undergoing PCI, which has equal or better efficacy outcomes without increasing the rates of bleeding episodes. Moreover, we found initial triple therapy to be unnecessary as it increased the risk of bleeding.

KEYWORDS:

Anticoagulation; Antiplatelet; Antithrombotic; Bleeding; Coronary intervention; Efficacy

PMID:
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84

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Outcomes of Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention Receiving an Oral Anticoagulant and Dual Antiplatelet Therapy: A Comparison of Clopidogrel Versus Prasugrel From the TRANSLATE-ACS Study.

Jackson LR 2nd[1], Ju C[2], Zettler M[3], Messenger JC[4], Cohen DJ[5], Stone GW[6], Baker BA[7], Effron M[3], Peterson ED[2], Wang TY[2].

Author information

Abstract

OBJECTIVES:

The purpose of this study was to determine whether bleeding risk varies depending on which P2Y12 receptor inhibitor agent is used.

BACKGROUND:

Prior studies have shown significant bleeding risk among patients treated with triple therapy (i.e., oral anticoagulant, P2Y12 receptor inhibitor, and aspirin).

METHODS:

We evaluated patients with acute myocardial infarction (MI) treated with percutaneous coronary intervention (PCI) at 233 hospitals in the United States enrolled in the TRANSLATE-ACS (Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) study (April 2010 to October

	2012). Using inverse probability-weighted propensity modeling, we compared 6-month adjusted risks of Bleeding Academic Research Consortium (BARC) bleeding, stratifying by whether or not bleeding was associated with rehospitalization among patients discharged on aspirin + anticoagulant + clopidogrel (triple-C), aspirin + anticoagulant + prasugrel (triple-P), aspirin + clopidogrel (dual-C), or aspirin + prasugrel (dual-P). ***RESULTS:*** Of 11,756 MI patients, 526 (4.5%) were discharged on triple-C, 91 (0.8%) on triple-P, 7,715 (66%) on dual-C, and 3,424 (29%) on dual-P. Compared with dual-therapy patients, triple-therapy patients had significantly higher any BARC-defined bleeding. Triple-P was associated with a greater risk of any BARC-defined bleeding events compared with triple-C. This finding was driven mostly by an increased risk of bleeding events that were patient-reported only and did not require rehospitalization. There were no significant differences in bleeding requiring rehospitalization between the triple-P and -C groups. ***CONCLUSIONS:*** Among MI patients, the addition of an oral anticoagulant was associated with a significantly greater risk of any BARC-defined bleeding relative to dual antiplatelet therapy, regardless of which P2Y12 receptor inhibitor was selected. Among patients on triple therapy, prasugrel use was associated with higher patient-reported-only bleeding, but not bleeding requiring rehospitalization, than clopidogrel-treated patients. ***KEYWORDS:*** P2Y(12) receptor inhibitor agents; bleeding risk; triple therapy **Comment in** • Do Not Use Novel Antiplatelet Agents in Patients on Oral Anticoagulants After Stenting. [JACC Cardiovasc Interv. 2015] PMID: 26718518 DOI: 10.1016/j.jcin.2015.08.018 [Indexed for MEDLINE] Free full text
140	Drug Saf. 2015 May;38(5):481-91. doi: 10.1007/s40264-015-0286-8. Risks and benefits of triple oral anti-thrombotic therapies after acute coronary syndromes and percutaneous coronary intervention. Alfredsson J[1], Roe MT.

	Author information **Abstract** The key pathophysiological process underlying symptomatic coronary artery disease, including acute coronary syndromes (ACS), is usually a rupture or an erosion of an atherosclerotic plaque, followed by platelet activation and subsequent thrombus formation. Early clinical trials showed benefit with long-term aspirin treatment, and later-based on large clinical trials-dual anti-platelet therapy (DAPT), initially with clopidogrel, and more recently with prasugrel or ticagrelor, has become the established treatment in the post-ACS setting and after percutaneous coronary intervention (PCI). Treatment with DAPT is recommended for both ST-elevation myocardial infarction and non-ST-elevation ACS, as well as after PCI with stenting, in American and European clinical guidelines. Notwithstanding the benefits observed with DAPT, including third-generation P2Y12 receptor inhibitors plus aspirin, ACS patients remain at high risk for a recurrent cardiovascular event, suggesting that other treatment strategies, including the addition of a third oral anti-platelet agent or a novel oral anticoagulant (NOAC) to standard DAPT regimens, may provide additional benefit for post-ACS patients and for patients undergoing PCI. Adding a third anti-thrombotic agent to DAPT after an ACS event or a PCI procedure has been shown to have modest benefit in terms of ischemic event reduction, but has consistently been associated with increased bleeding complications. Therefore, the quest to optimize anti-thrombotic therapies post-ACS and post-PCI continues unabated but is tempered by the historical experiences to date that indicate that careful patient and dose selection will be critical features of future randomized trials. PMID: 25829216 DOI: 10.1007/s40264-015-0286-8

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#1	Add	Search **triple therapy** Filters: **Meta-Analysis; Systematic Reviews; Randomized Controlled Trial; Humans**	2398	03:40:51

Ein- und Ausschluss der gefundenen 8 Studien:

Ausschluss:	
Darstellung nur von Leitlinien	2
Keine Original-Arbeiten	2
Kein Abstract, nicht auf Englisch/Deutsch verfügbar	1
Eingeschlossene Studien	3
	8

Nr	Arbeit	Ein-schluss	Begründung
1	Thromb Haemost. Faxon **Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective.** PMID: 21785808	Nein	A7
2	Chest. Zhao **"Triple therapy" rather than "triple threat": a meta-analysis of the two**	Ja	

	antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. PMID: 21285053		
3	Int J Cardiol. Gao **Meta-analysis of the combination of warfarin and dual antiplatelet therapy after coronary stenting in patients with indications for chronic oral anticoagulation.** PMID: 21185095	Ja	
4	EuroIntervention. Zahger **Coronary stenting in warfarin treated patients.** PMID: 19527984	Nein	A4
5	Ann Med. Rubboli **Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation.** PMID: 18608125	Ja	
6	Ann Pharmacother. Hermosillo **Aspirin, clopidogrel, and warfarin: is the combination appropriate and effective or inappropriate and too dangerous?** PMID: 18477734	Nein	A3
7	Lakartidningen. Wallén **["Triple therapy" with warfarin, clopidogrel and acetylsalicylic acid. High risk treatment with unclear benefit].** [Article in Swedish] PMID: 18193674	Nein	A5
8	Intern Emerg Med. Rubboli **Triple therapy of warfarin, aspirin and a thienopyridine for patients treated with vitamin K antagonists undergoing coronary stenting. A review of the evidence.** PMID: 17909705	Nein	A4

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