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SYSTEMATIC REVIEW

Are Generic Drugs Used in Cardiology as Effective and Safe as their Brand-name Counterparts? A Systematic Review and Meta-analysis

Jacinthe Leclerc[1,2,3] · Magalie Thibault[1] · Jennifer Midiani Gonella[1,4] · Claudia Beaudoin[3,5] · John Sampalis[2]

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Abstract

Background Previous systematic reviews (2008; 2016) concluded similarity in outcomes between brand-name and generic drugs in cardiology, but they included ≥ 50% comparative bioavailability studies, not designed or powered to detect a difference in efficacy or safety between drug types. We aimed to summarise best-evidence regarding the effectiveness and safety of generic versus brand-name drugs used in cardiology.

Methods For this systematic review of the literature, scientific databases (MEDLINE and EMBASE) were searched from January 1984 to October 2018. Original research reports comparing the clinical impact of brand-name versus generic cardiovascular drugs on humans treated in a real-life setting, were selected. Meta-analyses and subgroup analyses were performed. Heterogeneity (I^2) and risk of bias were tested.

Results Among the 3148 screened abstracts, 72 met the inclusion criteria ($n \geq 1{,}000{,}000$ patients, mean age 65 ± 10 years; 42% women). A total of 60% of studies showed no difference between drug types, while 26% concluded that the brand-name drug was more effective or safe, 13% were inconclusive and only 1% concluded that generics did better. The overall crude risk ratio of all-cause hospital visits for generic versus brand-name drug was 1.14 (95% confidence interval: 1.06–1.23; I^2: 98%), while it was 1.05 (0.98–1.14; I^2: 68%) for cardiovascular hospital visits. The crude risk ratio was not statistically significant for randomised controlled trials only ($n = 4$; 0.92 [0.63–1.34], I^2: 35%).

Conclusion The crude risk of hospital visits was higher for patients exposed to generic compared to brand-name cardiovascular drugs. However, the evidence is insufficient and too heterogeneous to draw any firm conclusion regarding the effectiveness and safety of generic drugs in cardiology.

Key Points

This systematic review and meta-analysis reports that more than half of studies showed no difference in outcomes between cardiovascular generics and the brand-name drugs.

The overall crude risk of hospital visits was higher for patients exposed to generics.

Even though evidence is insufficient and very heterogeneous to draw any firm conclusion, results signal that more studies are required to confirm the effectiveness and safety of international generic drug licensing processes.

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✉ Jacinthe Leclerc
Jacinthe.leclerc@uqtr.ca

1 Department of Nursing, Université du Québec à Trois-Rivières, 3351, boul. des Forges, C.P. 500, Local 4849, Santé, Trois-Rivières, QC G9A 5H7, Canada

2 Department of Surgery, McGill University, Montreal, Canada

3 Bureau d'information et d'études en Santé des Populations, Institut National de Santé Publique du Québec, Quebec City, Canada

4 Faculty of Nursing, Universidade de Sao Paulo, Ribeirao Preto, Brazil

5 Faculty of Medicine, Université Laval, Quebec City, Canada

1 Introduction

When a brand-name drug patent expires, generic drugs are commercialised at lower cost [1]. Health authorities regulate bioequivalence standards for generic drugs by comparative bioavailability studies. It is known and accepted that some bioavailability parameters for generic versions may vary up to 20% compared to the original reference drug [2]. This difference could potentially explain the occurrence of side effects or low efficacy for patients switched to generics [3–5], a fact already controversial in the literature [6, 7].

Two large systematic reviews and meta-analyses (2008; 2016) reported similar rates of hospital visits and clinical measurement outcomes between brand-name and generic users in cardiology [8, 9]. However, even though well conducted, the conclusions of these systematic reviews were based on the authors' meta-analyses, which included ≥ 50% of comparative bioavailability studies. Those studies are not designed or powered to detect a difference in efficacy or safety. Indeed, comparative bioavailability studies are generally crossover randomised controlled trials powered to detect a difference in bioavailability between drugs. A selected group of 12–50 healthy fasting subjects are administered a single dose of the tested generic and, after a washout period, a single dose of the brand-name reference product [2, 10]. The follow-up of subjects is normally < 72 h. We believe that including comparative bioavailability studies in these systematic reviews may have led to underestimation of the true difference between the groups.

Clinicians and researchers agree on the urgency to determine if generic drugs, licensed through healthcare policies, are as effective and safe as the brand-name products [11]. In the current study, we aimed to perform a synthesis of best evidence to answer the following question: "Are generic drugs used in cardiology as effective and safe as their brand-name counterparts?" The tested hypothesis is that there would be a difference in outcomes between generic and brand-name users. Results would then differ from previously published systematic reviews on this research question [8, 9].

2 Methods

2.1 Study Design

This is a systematic review of the literature following the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions [12]. Results are reported according to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [13].

2.2 Source of Data

The search was conducted online in MEDLINE and EMBASE. These electronic databases were searched from their inception or from January 1984 to October 2018, and an update was performed on July 2019.

2.3 Search Strategy

Similar to Kesselheim et al. [8], three main subject terms were used: (1) a term related to the type of study (e.g. clinical trial, retrospective cohorts, etc.), (2) a term related to the product of interest (e.g. generic, brand-name, etc.), (3) a term related to cardiovascular medicine (e.g. heart failure, beta-blockers, etc.; details in Supplementary Material). The search strategy was designed for MEDLINE and adapted for Embase. Abstracts containing at least one search item in each of the three main categories met criteria for the title and abstract review. References from identified studies and existing reviews were screened to complete the systematic search of studies. Every identified abstract was imported into Endnote (version X9, Thomson Reuters). Duplicates were removed.

2.4 Eligibility Criteria for Study Selection

Title and abstracts of each identified reference were screened independently by three reviewers (JL, MT and JMG) and selected for full-text review if they were original research reports comparing the clinical impact of brand-name versus generic cardiovascular drugs on humans treated in real-life setting (i.e. not in a pre-marketing, randomised clinical trial environment). Studies conducted with healthy subjects, using biological products or aiming at comparing pharmacokinetics parameters only, were excluded (more details in Supplementary material). Disagreements were discussed and resolved by consensus. Then, JL and MT assessed every full-text article to determine final inclusions.

2.5 Outcomes

Primary outcomes were clinical measures when available (systolic blood pressure [diastolic was not available], lipids level, heart rate, etc.) and all-cause hospital visits (including consultations at the emergency room [department], hospital admissions, specific cardiovascular disease-related hospital visits, etc.).

2.6 Data Extraction

Data were extracted by two independent reviewers (JL and MT). A pilot extraction was conducted on 10 studies of

various designs for training and to ensure further agreement on data extraction. A standardised data extraction form was used (see Items in Supplementary Material). Authors were contacted for missing data.

2.7 Risk of Bias

The risk of bias of each study was assessed by two independent reviewers using recommended tools: (1) the Cochrane method for randomised controlled trials [13] and (2) ROBINS-I for non-randomised controlled trials [14]. For the former, the judgement for each entry involves assessing the risk of selection, performance, detection, attrition and reporting bias as low, high or unclear (including lack of information or uncertainty). For the latter, the judgement regarding the risk of selection, information and confusion bias was made as low, moderate, serious, critical or "no information" [14]. Unlike Kesselheim et al. [8] and Manzoli et al. [9], we did not elect to use scales that yield a summary score, as this practice is now discouraged by the Cochrane Collaboration (2019). The risk of bias was impossible to assess for some studies due to lack of information (e.g. abstract only, article in Russian language).

2.8 Statistical Analyses

Descriptive analyses of main study characteristics were performed, and the proportions of studies with the following conclusions were calculated: (1) No difference; (2) Favours generics; (3) Favours brand-name; (4) Uncertain or various differences. We also performed a subgroup analysis to compare the distribution of authors' conclusion according to the type of publication (abstract vs full text).

Outcome data were aggregated using random effect meta-analyses. Crude association was expressed as risk ratio for hospital visit outcomes and mean difference for continuous clinical outcomes. Meta-analyses were performed using Review Manager (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Heterogeneity was tested with the I^2 statistic and interpreted with suggested thresholds (Low: 0–40%; Moderate: 30–60%; Substantial: 50–90%; Considerable heterogeneity: 75–100%) [13]. We constructed funnel plot to assess the risk of publication bias. Subgroup analyses were planned a priori and conducted according to the following variables: study design (randomised vs non-randomised control trials), publication type (abstract vs full text), follow-up duration, source of funding (industry, non-industry or not reported) and drug classes. Statistical significance was judged according to 95% confidence intervals.

3 Results

3.1 Characteristics of Studies

A total of 3148 abstracts were identified by the search strategy (Fig. 1). A set of 105 studies were then screened for final eligibility. Of those, 72 were included in the qualitative analysis (published as abstracts or full texts; 33 excluded due to non-English non-French language (6), duplicate studies of previously published abstracts (16) or not comparing brand-name to generic drugs (11). Among those, only 33 were included in the quantitative analysis as others had no extractable data in the abstracts or the full text for pooling. A total of 22 studies were funded by the pharmaceutical industry (Table 1). The risk of bias was modest to serious in the majority of studies (Table S1 and S2, Supplementary Material). There were 30 randomised clinical trials and 42 non-randomised clinical/observational studies. Follow-up time varied between < 1 day and 20 years (Table 1).

3.2 Patient Characteristics

The studies included a total of > 1,000,000 patients who used generic or brand-name cardiovascular drugs. Mean age was 65 ± 10 years old and 42% were women. The most commonly studied therapeutic classes were antiplatelets, statins, anticoagulants, angiotensin II receptor blockers and beta-blockers (Fig. 2). It was not possible to ascertain differences in patient characteristics according to generic or brand-name group due to unavailability of most granular data and to the heterogeneity of available information.

3.3 Comparison on Outcome Between Generics and the Brand-name

A total of 43 studies (60%) showed no difference between generic and brand-name drugs, while 19 studies (26%) concluded that the brand-name drug was more effective or safe than the generic drug. Nine studies (13%) were inconclusive and only one (1%) concluded that generics were more safe or effective than the brand-name drug.

The only extractable clinical and hospital visits data for the meta-analyses were platelet function (including relative or absolute value of platelet aggregation when available), systolic blood pressure, international normalised ratio and hospital visits (all-cause and cardiovascular hospitalisations or emergency department visits). The overall crude risk ratio of all-cause hospital visits was 1.14 (1.06–1.23), while it was 1.05 (0.98–1.14) for cardiovascular hospital visits (Fig. 3a). The pooled "Hospital visits" outcome yielded a crude risk ratio of 1.10 (1.04–1.15). Platelet function (Fig. 3b),

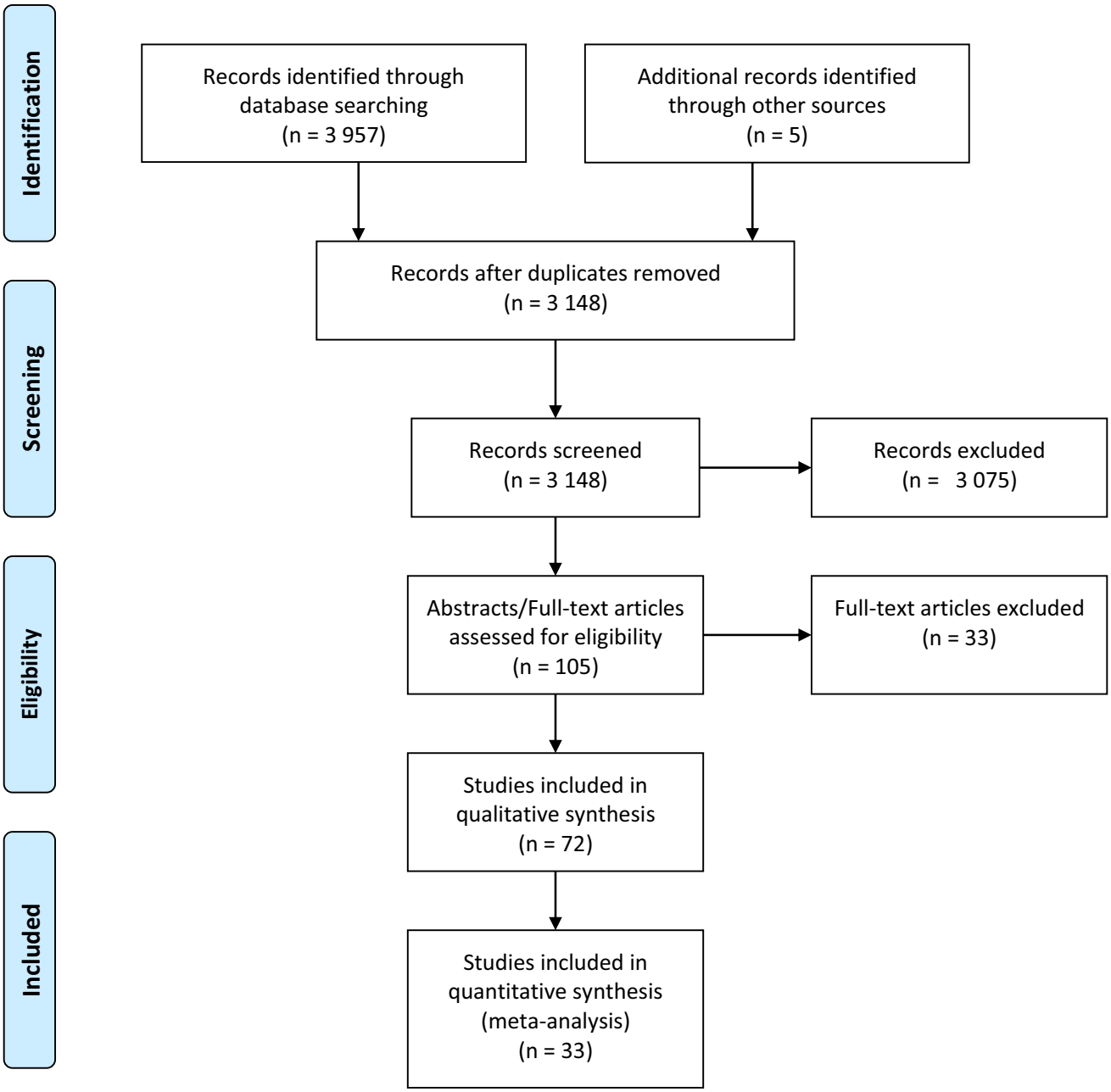


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

international normalised ratio (Fig. 3c) and systolic blood pressure (Fig. 3d) were similar between generic and brand-name groups. Heterogeneity was substantial to considerable in all meta-analyses (I^2: 60–96%; Fig. 3), except for the systolic blood pressure (I^2: 15%).

In the first sensitivity analysis, the crude risk ratio of all-cause hospital visits was statistically significant for non-randomised controlled trials (1.10 [1.05–1.16]), while it was not for randomised controlled trials (0.92 [0.63–1.34], Fig. S1-A). Following sensitivity analyses revealed that the risk ratio of hospital visits was: (1) still statistically significant when excluding abstract-only studies (1.10 [1.04–1.16], Fig. S1–B) and, (2) statistically significant in both studies with a follow-up of ≤ 2 months (3.13 [1.14–8.55]) or those with > 2 months (1.09 [1.04–1.15]), Fig. S1–C). The risk ratio of hospital visits was not statistically significant in studies funded by the industry (1.07 [0.96–1.19], Fig. S1–D), while it was statistically significant in studies not funded by the industry (1.11 [1.03–1.19]) or those for which the funding was not disclosed (1.09 [1.03–1.16]). Last, the risk ratio of hospital visits differed according to drug classes: 1.08 for antiplatelets [0.90 to 1.29], 0.93 for statins [0.86–1.02],

Table 1 Studies included in the review ($n=72$)

Source (first author; year of publication)	Type of publication	Drugs studied	Number of patients	Mean age	Follow-up (days)	Source of funding	Outcomes	Final interpretation
Sharoky et al. (1989) [19]	Abstract	Hydrochlorothiazide	30	n/a	42	n/a	Blood pressure	No difference
Saseen et al. (1997) [20]	Article	Verapamil	8	70	14	Government/academia	Blood pressure	Various differences
Neutel et al. (1998) [21]	Abstract	Warfarin	39	n/a	63	n/a	INR	No difference
Swenson et al. (2000) [22]	Article	Warfarin	210	79	56	Industry	INR	No difference
Assawawitoontip et al. (2002) [23]	Article	Simvastatin	34	37	140	Industry	Lipids level	No difference
Milligan et al. (2002) [24]	Article	Warfarin	182	75	540	Industry	INR	No difference
Ol'binskaia et al. (2003) [25]	Abstract	Simvastatin	n/a	n/a	56	n/a	Lipids level	No difference
Witt et al. (2003) [26]	Article	Warfarin	2299	69	90	n/a	INR	Favours brand-name
Ashraf et al. (2005) [27]	Article	Clopidogrel	35	49	0.5	Industry	Platelet aggregation	No difference
Lee et al. (2005) [28]	Article	Warfarin	34	52	84	None	INR	No difference
Pereira et al. (2005) [29]	Article	Warfarin	7	63	210	n/a	INR	No difference
Ahrens et al. (2007) [30]	Article	Metoprolol	49,673	56	457	Industry	Hospitalisation due to myocardial infarction, hypertensive crisis and stroke	No difference
Kim et al. (2007) [31]	Article	Amlodipine	188	53	56	Industry	Blood pressure	No difference
Tran et al. (2007) [32]	Abstract	Statins	2268	n/a	365	n/a	Lipids level	Favours brand-name
Loebstein et al. (2008) [33]	Article	Rosiglitazone	1046	63	270	n/a	HbA1c	No difference
Tsinamdzgvrishvili et al. (2008) [34]	Abstract	Amlodipine	20	n/a	n/a	n/a	Blood pressure	No difference
Kim et al. (2009) [35]	Article	Ramipril	89	50	56	Industry	Blood pressure	No difference
Jeong et al. (2010) [36]	Article	Clopidogrel	20	61	180	Industry	Platelet aggregation	Various differences
Kim et al. (2010) [37]	Article	Atorvastatin	211	62	56	Industry	Lipid level	No difference
Sicras et al. (2010) [38]	Article (Russian)	Amlodipine	620	74	730	Industry	Blood pressure	Favours brand-name
Boh et al. (2011) [39]	Abstract	Atorvastatin	148	n/a	84	n/a	Coronary risk	No difference

Table 1 (continued)

Source (first author; year of publication)	Type of publication	Drugs studied	Number of patients	Mean age	Follow-up (days)	Source of funding	Outcomes	Final interpretation
Ghate et al. (2011) [40]	Article	Warfarin	37,756	71	1460	Industry	Hospitalisation for thrombotic events	Favours brand-name
Khosravi et al. (2011) [41]	Article	Clopidogrel	442	59	730	Industry	MACE	No difference
Tsadok et al. (2011) [42]	Article	Amiodarone	9082	77	1642.5	Government/ academia	Thyroid dysfunction	No difference
Bobrova et al. (2012) [43]	Article (Russian)	Enalapril	40	75–90	28	n/a	Blood pressure	Favours brand-name
Fukuhara et al. (2012) [44]	Article	Nifedipine	77	n/a	56	n/a	Blood pressure	No difference
Grigor'eva et al. (2012) [45]	Abstract	Bisoprolol	102	n/a	84	n/a	Endothelial function	Favours brand-name
Kwong et al. (2012) [46]	Article	Warfarin	12,908	67	365	Industry	All-cause hospitalisation, ED visits	Favours brand-name
Martsevich et al. (2012) [47]	Article (Russian)	Various drugs for ischaemic heart disease	120	59	84	n/a	Blood pressure	Various differences
Oberhansli et al. (2012) [48]	Article	Clopidogrel	60	69	40	Private Foundation	Platelet reactivity	No difference
Park et al. (2012) [49]	Article	Clopidogrel	428	62	365	n/a	MACE	No difference
Solangi et al. (2012) [50]	Article	Simvastatin	264	n/a	84	n/a	Lipids level	No difference
Srimahachota et al. (2012) [51]	Abstract	Clopidogrel	49	n/a	0.25	n/a	Platelet aggregation	No difference
Tsoumani et al. (2012) [52]	Article	Clopidogrel	86	71	180	n/a	Platelet aggregation	No difference
Colombo et al. (2013) [53]	Article	Metformin	75,423	66	1020	Industry	All-cause hospitalisation	No difference
Haas et al. (2013) [54]	Abstract	Statins	1411	64	2555	n/a	Lipids level	Various differences
Huang et al. (2013) [55]	Article	Fenofibrate	114	65	180	n/a	Lipids level	Favours brand-name
Kalo et al. (2013) [56]	Abstract	Losartan	2727	n/a	1095	n/a	MACE	No difference
Malyhina et al. (2013) [57]	Article (Russian)	Perindopril	40	35–75	61	n/a	Blood pressure	No difference
Martsevich et al. (2013) [58]	Article (Russian)	Bisoprolol and hydrochlorothiazide	30	63	126	n/a	Blood pressure	No difference
Szczotka et al. (2013) [59]	Abstract	Ramipril	120	n/a	1	n/a	Blood pressure	Favours brand-name
Tsivgoulis et al. (2013) [60]	Abstract	Clopidogrel	47	70	540	n/a	Platelet aggregation	Favours brand-name
Balandina et al. (2014) [61]	Abstract	Simvastatin	55	n/a	28	n/a	Lipids level	Favours brand-name

Table 1 (continued)

Source (first author; year of publication)	Type of publication	Drugs studied	Number of patients	Mean age	Follow-up (days)	Source of funding	Outcomes	Final interpretation
Corrao et al. (2014) [62]	Article	Simvastatin	13,799	63	1278	Academia	Hospitalisation for CV events	No difference
Corrao et al. (2014) [63]	Article	ACEIs, ARBs, Antisympathetic agents	4412	59	2190	Industry	Hospitalisation for CV disease	No difference
Gagne et al. (2014) [64]	Article	Lovastatin, Pravastatin, Simvastatin	90,111	76	365	Industry	MACE	Favours generics
Kovacic et al. (2014) [65]	Article	Clopidogrel	11,284	65	30	Industry	Hospitalisation for stent thrombosis	Favours brand-name
Maskon et al. (2014) [66]	Abstract	Clopidogrel	64	n/a	30	n/a	Platelet suppression	Various differences
Seo et al. (2014) [67]	Article	Clopidogrel	90	58	0.083	Industry	Platelet reactivity	No difference
Syvolap et al. (2014) [68]	Article	Clopidogrel	33	54	21	n/a	Platelet aggregation	Favours brand-name
Vichairuangthum et al. (2014) [69]	Abstract	Enoxaparin	66	65	0.04167	n/a	MACE	Favours brand-name
Hamilos et al. (2015) [70]	Article	Clopidogrel	101	64	0.583	Industry	Platelet reactivity	No difference
Komosa et al. (2015) [71]	Article	Clopidogrel	53	49	8	Industry	Platelet aggregation	No difference
Choo et al. (2016) [72]	Abstract	Warfarin	23,141	n/a	1825	n/a	Hospitalisation for stroke	Various differences
Hellfritzsch et al. (2016) [73]	Article	Warfarin	105,751	72	660	none	Hospitalisation for bleeding	Favours brand-name
Jackevicius et al. (2016) [7]	Article	Statins	15,726	77	365	Private Foundation	MACE	No difference
Malinova et al. (2016) [74]	Abstract	Clopidogrel	543	n/a	180	n/a	Platelet aggregation	Various differences
Ntalas et al. (2016) [75]	Article	Clopidogrel	1557	70	365	Industry	MACE	No difference
Tarlovskaya et al. (2016) [76]	Abstract	Bisoprolol	61	n/a	42	n/a	Heart rate	No difference
Hajizadeh et al. (2017) [77]	Article	Clopidogrel	129	58	30	Academia	Platelet aggregation	No difference
Lee et al. (2017) [78]	Article	Atorvastatin	346	63	56	Industry	Lipids level	No difference
Loch et al. (2017) [79]	Article	Atorvastatin	266	64	90	None	Lipids level	No difference
Leclerc et al. (2017) [80]	Article	Losartan, valsartan, candesartan	136,177	76	1095	None	All-cause hospitalisation and emergency room consultation	Favours brand-name

Table 1 (continued)

Source (first author; year of publication)	Type of publication	Drugs studied	Number of patients	Mean age	Follow-up (days)	Source of funding	Outcomes	Final interpretation
Pollak et al. (2017) [81]	Article	Nifedipine	20	64	14	n/a	Blood pressure	Favours brand-name
Chanchai et al. (2018) [82]	Article	Carvedilol, Bisoprolol	217	58	168	Academia	Beta-blocker target dose	No difference
Desai et al. (2018) [83]	Abstract	Warfarin	33,645	77	n/a	n/a	MACE	No difference
Dinic et al. (2018) [84]	Abstract	Antihypertension drugs	43	61	42	n/a	Blood pressure	No difference
Gengo et al. (2018) [85]	Abstract	Clopidogrel	439	n/a	14	Private	Platelet aggregation	Various differences
Ko et al. (2018) [6]	Article	Clopidogrel	24,530	77	365	Private foundation	MACE	No difference
Leclerc et al. (2018) [4]	Article	Warfarin	280,158	58	7300	None	All-cause hospitalisation and emergency room consultation	Favours brand-name
Povetkin et al. (2018) [86]	Article (Russian)	Ivabradine	20	n/a	56	n/a	Heart rate	No difference
Leclerc et al. (2019) [3]	Article	Clopidogrel	89,525	78	1095	None	All-cause hospitalisation and emergency room consultation	Favours brand-name

ACEI angiotensin-converting-enzyme inhibitor, *ARB* angiotensin II receptor blocker, *HbA1c* haemoglobin A1C, *Industry* includes generic and brand-name manufacturers, *INR* international normalised ratio, *MACE* major adverse cardiovascular events

1.09 for anticoagulants [1.03–1.14] and 1.20 [1.17–1.23] for "others" (three angiotensin II receptor blockers and one beta-blocker, Fig. S1–E).

3.4 Risk of Publication Bias

The comparison between the distribution of proportions among authors' conclusions while excluding abstracts versus our main analysis, yielded statistically significant differences in proportions ($p = 0.0164$). The Funnel plots are modestly asymmetrical (Figs S2, Supplementary Material).

4 Discussion

4.1 Major Findings

In this systematic review, 60% of the studies showed similar effectiveness or safety between generic and brand-name cardiovascular drugs; approximately 30% showed brand-name drugs to be superior. There was no difference in platelet functions, international normalised ratio and systolic blood pressure between generic and brand-name drug users. However, we found a crude 10% higher risk of all-cause hospital visits compared to brand-name users. To our knowledge, this is the first systematic review of the literature reporting some differences in hospital visits between generics and brand-name drugs in cardiology.

Our results differ from previously published systematic reviews assessing equivalence of generic and brand-name drugs in cardiology [8, 9]. These reviews did not detect any difference in outcomes for generic versus brand-name cardiovascular drugs users, while we report that there may be some differences. Two main reasons could explain this discrepancy. First, we think previously published systematic reviews underestimated the true difference between groups due to the type of studies included. Indeed, half of the studies included in the Kesselheim et al. article [8] were comparative bioavailability studies. As mentioned earlier, those studies are not powered or designed to detect lack of efficacy/adverse events and definitely cannot be used to ascertain that generic drugs are equivalent to brand-name drugs in real-life settings. The subsequent paper of Manzoli et al. included only randomised clinical

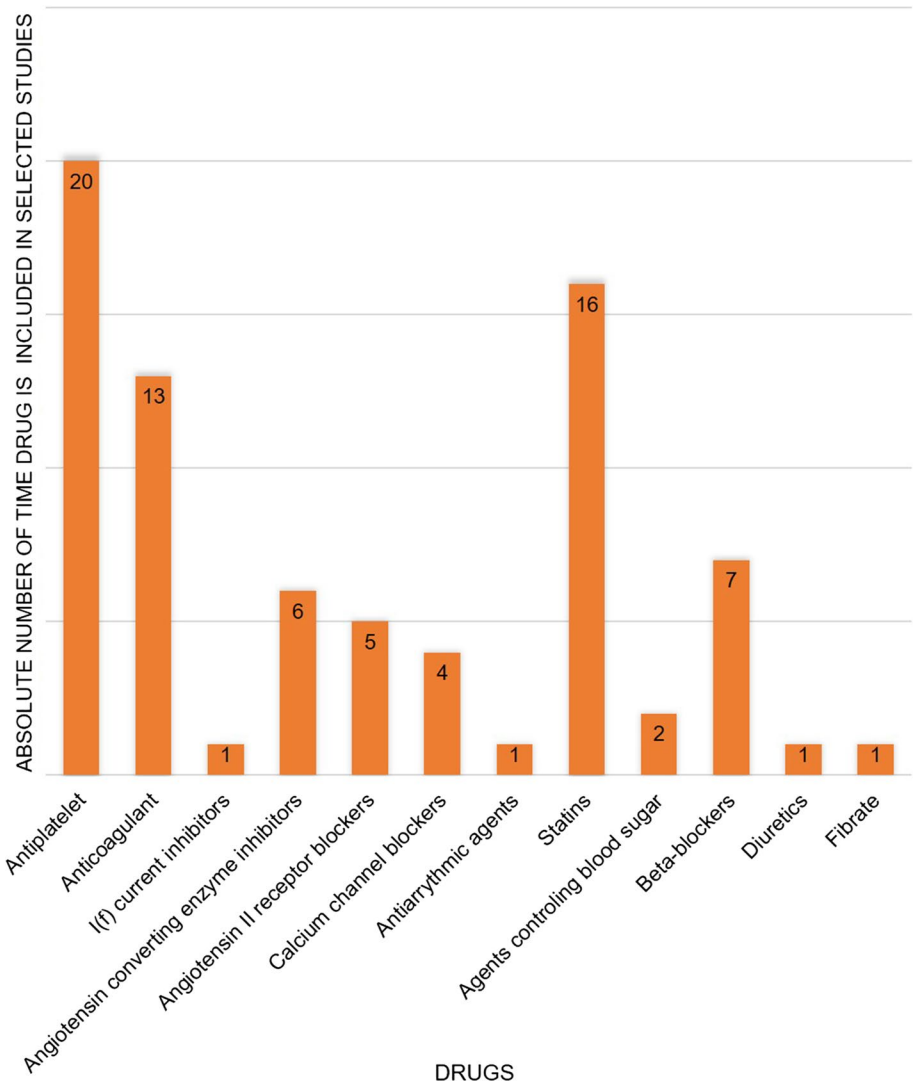


Fig. 2 Drugs in included studies

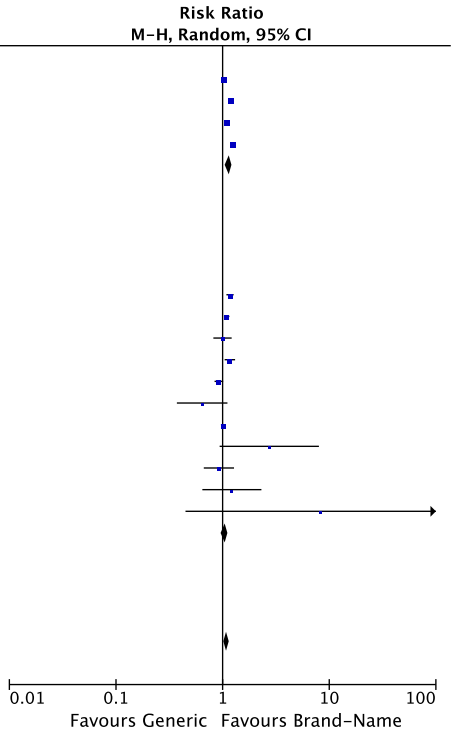
trials ($n = 74$), 42 of which are comparative bioavailability studies conducted in healthy subjects [9]. The second reason explaining discrepancies between our results and previously published similar systematic reviews is the addition of new scientific evidence in recent years. Among others, a research group from Ontario (Canada) published two well-conducted cohort studies comparing hospital admissions and mortality between generic and brand-name atorvastatin [7] and clopidogrel users [6]. No differences between groups were found in those studies but the substitution itself was not assessed. On the other hand, a group from Quebec (Canada) published 3 articles containing 5 time series analyses and over 500,000 patients using generic or brand-name losartan, valsartan, candesartan, warfarin or clopidogrel [3–5]. Those studies reported an 8–21% increase in rates of emergency room consultations or hospital admissions for the population switched to generic versions compared to patients who remained on the brand-name drug. The authors report that it was not possible to adjust the rates or the segmented regression models for potential confounders with this study design, but they performed many sensitivity analyses to test the robustness of the results.

4.2 Confounding Bias?

The risk ratio of all-cause hospital visits was statistically significant for non-randomised controlled trials, but not for randomised controlled trials, suggesting that results from non-randomised controlled trials are biased by confounders. If true, this would probably lead to an overestimation of the risk ratio of hospital visits between generic and brand-name users. Other factors seemed to impact the risk ratio estimated in our meta-analysis (follow-up duration, drug classes). Unfortunately, we were not able to perform meta-regression due to the heterogeneity of the information available in the articles and to the small amount of studies per subgroup.

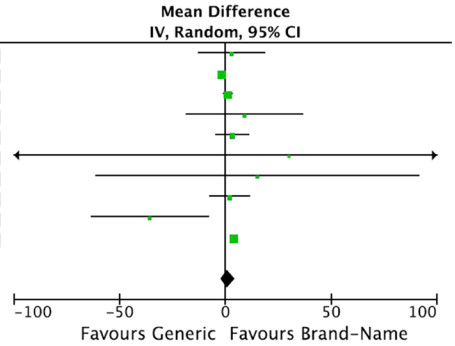
A

Study or Subgroup	Generic Events	Generic Total	Brand-Name Events	Brand-Name Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Studies Reporting All-Cause Hospital Visits						
Kwong et al. 2012	9700	12117	971	1241	11.4%	1.02 [0.99, 1.05]
Leclerc et al. 2017	8281	35554	8395	43428	11.5%	1.20 [1.17, 1.24]
Leclerc et al. 2018	89398	172917	283938	607325	11.9%	1.11 [1.10, 1.11]
Leclerc et al. 2019	8598	20594	8214	24773	11.6%	1.26 [1.23, 1.29]
Subtotal (95% CI)		**241182**		**676767**	**46.6%**	**1.14 [1.06, 1.23]**
Total events	115977		301518			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 173.18$, df = 3 ($P < 0.00001$); $I^2 = 98\%$						
Test for overall effect: $Z = 3.54$ ($P = 0.0004$)						
1.9.2 Studies Reporting Specific Cardiovascular-Related Hospital Visits						
Ahrens et al. 2007	777	7488	2137	24156	9.2%	1.17 [1.09, 1.27]
Choo et al. 2016	2257	12944	1629	10197	10.3%	1.09 [1.03, 1.16]
Corrao et al. 2014	265	8840	149	4959	4.1%	1.00 [0.82, 1.22]
Ghate et al. 2011	1431	18730	351	5372	7.4%	1.17 [1.04, 1.31]
Jackevicius et al. 2016	772	7863	838	7863	8.4%	0.92 [0.84, 1.01]
Khosravi et al. 2011	19	212	29	208	0.8%	0.64 [0.37, 1.11]
Ko et al. 2018	2128	11887	2225	12643	10.5%	1.02 [0.96, 1.07]
Kovacic et al. 2014	4	1054	20	14432	0.2%	2.74 [0.94, 8.00]
Ntalas et al. 2016	65	798	67	759	1.9%	0.92 [0.67, 1.28]
Park et al. 2012	19	211	16	217	0.6%	1.22 [0.65, 2.31]
Vichairuangthum et al. 2014	3	30	0	36	0.0%	8.35 [0.45, 155.61]
Subtotal (95% CI)		**70057**		**80842**	**53.4%**	**1.05 [0.98, 1.14]**
Total events	7740		7461			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 30.82$, df = 10 ($P = 0.0006$); $I^2 = 68\%$						
Test for overall effect: $Z = 1.41$ ($P = 0.16$)						
Total (95% CI)		**311239**		**757609**	**100.0%**	**1.10 [1.04, 1.15]**
Total events	123717		308979			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 212.29$, df = 14 ($P < 0.00001$); $I^2 = 93\%$						
Test for overall effect: $Z = 3.63$ ($P = 0.0003$)						
Test for subgroup differences: $Chi^2 = 2.34$, df = 1 ($P = 0.13$), $I^2 = 57.3\%$						



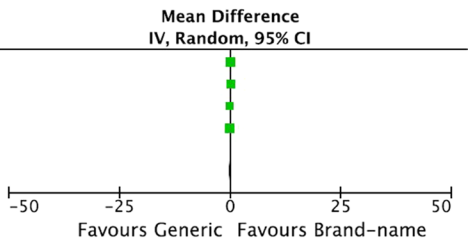
B

Study or Subgroup	Generic Mean	Generic SD	Generic Total	Brand-Name Mean	Brand-Name SD	Brand-Name Total	Weight	Mean Difference IV, Random, 95% CI
Ashraf et al. 2005	60.7	30.8	30	57.8	31.4	30	4.2%	2.90 [-12.84, 18.64]
Gengo et al. 2018	3.32	4.03	185	5.09	4.55	254	24.9%	-1.77 [-2.58, -0.96]
Hajizadeh et al. 2017	14.8	5.8	58	13.7	7	68	22.9%	1.10 [-1.14, 3.34]
Hamilos et al. 2015	204	67	51	195	74	50	1.6%	9.00 [-18.55, 36.55]
Jeong et al. 2010	39.8	16.2	20	36.5	7.9	20	11.2%	3.30 [-4.60, 11.20]
Komosa et al. 2015	239	329	28	209	406	25	0.0%	30.00 [-170.45, 230.45]
Maskon et al. 2014	-32.42	185.49	31	-47.48	116.41	33	0.2%	15.06 [-61.37, 91.49]
Oberhansli et al. 2012	33	28	60	31	25	60	9.0%	2.00 [-7.50, 11.50]
Seo et al. 2014	231.1	71.3	47	266.9	67.4	48	1.5%	-35.80 [-63.71, -7.89]
Sylovap et al. 2014	28	2.5	33	23.9	2.1	33	24.6%	4.10 [2.99, 5.21]
Total (95% CI)			**543**			**621**	**100.0%**	**1.13 [-2.41, 4.67]**
Heterogeneity: $Tau^2 = 12.96$; $Chi^2 = 78.31$, df = 9 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: $Z = 0.62$ ($P = 0.53$)								



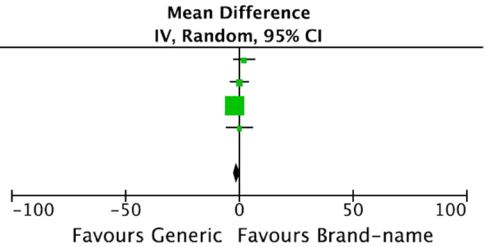
C

Study or Subgroup	Generic Mean	Generic SD	Generic Total	Brand-Name Mean	Brand-Name SD	Brand-Name Total	Weight	Mean Difference IV, Random, 95% CI
Lee et al. 2005	2.28	0.06	34	2.27	0.06	34	27.5%	0.01 [-0.02, 0.04]
Neutel et al. 1998	2.43	0.051	20	2.238	0.183	19	24.4%	0.19 [0.11, 0.28]
Swenson et al. 2000	2.7	0.5	105	2.8	0.5	105	20.5%	-0.10 [-0.24, 0.04]
Witt et al. 2003	2.41	0.45	2299	2.54	0.51	2299	27.5%	-0.13 [-0.16, -0.10]
Total (95% CI)			**2458**			**2457**	**100.0%**	**-0.01 [-0.13, 0.11]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 80.27$, df = 3 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: $Z = 0.11$ ($P = 0.91$)								



D

Study or Subgroup	Generic Mean	Generic SD	Generic Total	Brand-Name Mean	Brand-Name SD	Brand-Name Total	Weight	Mean Difference IV, Random, 95% CI
Fukuhara et al. 2012	150	16	77	148	14	77	10.2%	2.00 [-2.75, 6.75]
Kim et al. 2007	128	15	80	128	10	81	14.2%	0.00 [-3.94, 3.94]
Pollak et al. 2017	133	2	20	135	2	20	68.4%	-2.00 [-3.24, -0.76]
Sharoky et al. 1989	129	9	15	129	7	15	7.1%	0.00 [-5.77, 5.77]
Total (95% CI)			**192**			**193**	**100.0%**	**-1.16 [-2.75, 0.42]**
Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 3.52$, df = 3 ($P = 0.32$); $I^2 = 15\%$								
Test for overall effect: $Z = 1.44$ ($P = 0.15$)								



◂**Fig. 3** Meta-analyses of hospital visits, platelet function, international normalised ratio and systolic blood pressure. **a** Cardiovascular and all-cause hospital visits. **b** Platelet function. **c** International normalised ratio. **d** Systolic blood pressure

4.3 Publication Bias?

It is interesting to note that only 70% of eligible records made it to publication of a full text article (Table 1). There was a statistically significant difference in proportions when comparing our qualitative analyses including and excluding abstracts. Nevertheless, it is reassuring to see that the overall qualitative interpretation of our results was similar in both classifications. In comparison, in 2016, Flacco et al. reported that fewer than 50% of registered protocols comparing a generic to a brand-name drug have ever had fully published results [15], and most of those were comparative bioavailability studies funded by generic manufacturers. The presence of a publication bias among generic versus brand-name scientific evidences is therefore possible even if it is difficult to detect in the Funnel plots. The presence of such a bias would be associated with an underestimation of true difference in outcomes between generic and brand-name drug users in cardiology.

4.4 Strengths and Limitations

Our review included the whole range of oral cardiovascular drug classes, even though some drug classes are underrepresented [e.g. *I*(*f*) current inhibitor]. Generalisability of the results should mostly apply to well-represented drug classes like antiplatelet, anticoagulants and statins. Another strength of this review is the inclusion of comprehensive real-world evidence on clinical equivalence. The related limitation of this feature is revealed by meta-analyses, reporting very high heterogeneity of included studies (only 15 studies with hospital visits extractable data for meta-analysis, and among those, only 4 reporting specific cardiovascular-related hospital visits), affecting the ability to draw firm conclusions on study results. Another limitation of our meta-analysis is the possibility of confounding bias; those are crude results and meta-regression was not possible as discussed above. As well, only 33 of 72 included records could be included in meta-analyses, mostly due to the presence of many abstracts with unextractable data. Meta-analyses may thus not fully reflect the literature (published and unpublished). Therefore, pooled differences in outcomes should be interpreted cautiously, notably regarding platelet aggregation for which no standardised value was used to pool studies. Despite these limitations, the results of our review are based on an exhaustive literature search and rigorous methodology.

4.5 Implications

The field of generic drug equivalence is very challenging due, among others things, to (1) the globalisation of raw ingredients/finished products (pills) manufacturers, governed by various jurisdictions worldwide, (2) the variable enforcement power of health authorities regarding good manufacturing practices [2], and the sparsity of sufficiently powered randomised controlled trials. Nevertheless, this systematic review highlights that the safety and effectiveness of generic cardiovascular drugs is uncertain. The biological plausibility of experiencing adverse events or lack of efficacy after switching from the brand-name to a generic version (or vice versa) has already been published [5, 16], but is still subject to debate [11]. Healthcare professionals, as well as patients, should be aware of the potential effects of generic substitution and report any adverse event or lack of efficacy to health authorities, such as Health Canada MedEffect system or the Food and Drug Administration Adverse Event Reporting System [17, 18]. The results of this review suggest that international generic drug licensing processes [2, 10] may need to be further challenged.

5 Conclusion

In the current analysis, 60% of the studies showed similar effectiveness or safety between generic and brand-name cardiovascular drugs; approximately 30% showed brand-name drugs to be superior. Overall, our results differ from previously published systematic reviews, but evidence is insufficient and too heterogeneous to support that generics are as effective and safe as brand-name drugs in cardiology. In particular, the crude risk ratio was not statistically significant between groups from randomised controlled trials only. More studies are then required to reassure patients, clinicians, researchers, payers and governments that actual generic drugs licensing processes are safe for the population taking generic drugs.

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Compliance with Ethical Standards

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Conflict of interest JS is a professor of medicine at McGill University and serves as the Chief Scientific Officer at JSS Medical Research, a contract research organisation that executes clinical trials/studies for pharmaceutical and biotechnology companies, as well as universities and hospitals. JL is a professor of nursing at Université du Québec à Trois-Rivières. Within her role of professor, she provides (1) Continuous Medical Education sessions for health care professionals, accredited by the Fédération des médecins omnipraticiens du Québec and its local affiliates and (2) statistical expertise on Data Safety Monitoring Board Committees managed by JSS Medical Research. Other authors have no conflict of interest to declare.

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