Int J Clin Exp Med 2019;12(4):3546-3557
www.ijcem.com /ISSN:1940-5901/IJCEM0079216

Original Article

Risk of gastrointestinal events during neratinib therapy in patients with cancer: a systematic review and meta-analysis of clinical trials

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Received August 5, 2017; Accepted November 10, 2018; Epub April 15, 2019; Published April 30, 2019

Abstract: Neratinib, an orally administered irreversible pan-ErbB receptor tyrosine kinase inhibitor, has been associated with overall incidence and risk of gastrointestinal (GI) events. This meta-analysis was performed to evaluate overall incidence and risk ratios (RR) of GI events associated with neratinib. PubMed and EMBASE were searched, along with conference abstracts published by the American Society of Clinical Oncology (ASCO). Eligible studies included prospective phase I or phase II clinical trials and expanded-access programs (outside a clinical trial) of patients with cancers assigned with neratinib. Outcomes included overall incidence and RR of GI events treated with neratinib. Statistical analyses were performed using Review Manager Version 5.3 and R 2.13.2 Meta package. A total of 12 studies, including 1,167 patients, were included in the meta-analysis. Meta-analysis of RR showed that neratinib was associated with a significantly increased risk of diarrhea (all-grade: RR 1.18, 95% CI 1.04-1.33 and high-grade: RR 1.47, 95% CI 1.07-2.00), vomiting (all-grade: RR 1.47, 95% CI 1.07-2.00 and high-grade: RR 1.45, 95% CI 1.07-1.98), and anorexia (all-grade: RR 4.47, 95% CI 2.24-8.90 and high-grade: RR 16.93, 95% CI 3.31-86.53), but risk of nausea (all-grade: RR 1.52, 95% CI 0.74-3.14 and high-grade: RR 2.53, 95% CI 0.83-7.70) was not increased. In conclusion, the most frequent GI events associated with neratinib were diarrhea, nausea, vomiting, and anorexia. This study revealed a significantly increased risk of diarrhea, vomiting, and anorexia with neratinib, compared with controls, suggesting that appropriate prevention and management should be performed.

Keywords: Neratinib, cancer, gastrointestinal events, risk, meta-analysis

Introduction

Neratinib (HKI-272), an irreversible tyrosine kinase inhibitor (TKI) which interrupts the pan-ErbB receptor, is an orally active drug for breast cancer and other solid tumors [1, 2]. Although neratinib is well tolerated in many patients, it is not devoid of side-effects. Several clinical trials have reported that common gastrointestinal (GI) events, including diarrhea, anorexia, nausea, and vomiting, are frequently associated with the use of TKIs in daily clinical practice [3]. It is of great importance to recognize and manage GI toxicities of patients treated with neratinib. It can affect therapeutic effects and quality of life of patients, leading to infection, discomfort, and mental burden for patients [4-6]. GI reactions may be alleviated with dose reduction and interruption, but these would also reduce the efficiency of neratinib. Additionally, it has been shown that severity of GI toxicities is correlated with efficiency of the drug.

Therefore, there is a need to master the characteristic features, incidence, and relative risk (RR) of GI events to aid prevention and intervention [7]. In this study, a meta-analysis was performed to assess the incidence and RR of GI events associated with neratinib-treated patients with cancer, providing treatment recommendations for these symptoms.

Materials and methods

Data sources and search strategy

PubMed, EMBASE, and Cochrane Library databases were searched from January 1964 to

January 2017, using the key words "neratinib" and "cancer", as well as "clinical trials". In addition, abstracts that contained "neratinib", presented at major meetings from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology, and the World Lung Cancer Conference, from 2004 to 2016, were searched. Full publications (not abstracts) from the Web of Science database were also examined to ensure that there were no additional studies.

Study selection

Inclusion criteria: (1) Prospective phase I or phase II clinical trials associated of neratinib-treated patients with cancer; (2) Assignment of participants to treatment with neratinib as a single agent, with no surgery, radiotherapy, or other treatments; and (3) Data available for incidence of GI events from patients. Exclusion criteria: (1) Investigations unrelated to the study drug; and (2) Original studies that me criterion (1) but with zero GI events.

Data extraction

Extracted information included first author, number of patients enrolled in the study, treatment information, and characteristics of the participants. GI events were regarded as clinical endpoints in this analysis, according to the outcomes of clinical trials with neratinib. To analyze the risk of GI events associated with neratinib, many adverse events (all-grade and high-grade included grade 3 or above) were collected.

Quality assessment

To determine the validity of selected studies, a modified Jadad scale was used to assess quality. High quality studies had scores of 4-8, whereas low quality studies had scores of 0-3. For non-randomized studies, the Newcastle-Ottawa Quality Assessment Scale was used. Each study was graded as either low quality (0-5) or high quality (6-9).

Statistical analysis

Meta-analyses were carried out using Review Manager Version 5.3 and R 2.13.2 Meta package. Pooled RR (Risk Ratio) estimates and 95% confidence intervals (CIs), stratified by study-setting and gender, were conducted using a random- or fixed-effects model, with between study heterogeneity assessed using the I^2 statistic. If I^2 was ≥50%, a random-effects model was used. Otherwise, a fixed-effects model was used. Median (min-max) values, mean ± standard deviation, and qualitative data regarding the number and percentage are given as descriptive statistics. Statistical significance was defined as a *P*-values < 0.05. All 95% CIs were two-sided. Finally, publication bias was quantitatively tested through application of Begg's test and Egger's test.

Results

Search results

The literature search yielded a total of 115 assessable publications. Of these, 12 relevant clinical trials [9-20] with neratinib, including a total of 4,197 patients, were included. **Figure 1** illustrates how the 12 studies were obtained from the literature search. The 12 selected studies were published between 2012 and 2015, including 4 phase I studies, 5 phase II studies, and 3 phase I/II studies. In all studies, the starting dose and schedule of neratinib was based on US FDA guidelines (daily oral 160 or 240 mg neratinib). Main characteristics of the studies are listed in **Table 1**. Jadad scores of the 12 studies included in the meta-analysis are listed for each trial in **Table 1**. The mean score was 4.25 (range, 3-6), indicating that overall study quality was fair.

Incidence of diarrhea

Analysis of overall incidence of all-grade diarrhea with neratinib was performed for 11 trials [9-17, 19, 20], including 993 patients. Incidence of all-grade diarrhea ranged from 29% to 95% for neratinib-treated patients with cancer. Interstudy heterogeneity testing showed significant results ($P < 0.0001$; $I^2 = 91.3\%$). Random-effects model meta-analysis indicated that overall incidence of all-grade diarrhea was 78.00% (95% CI 0.66-0.87) in patients assigned to neratinib (**Figure 2A**, **Table 2**). High-grade diarrhea associated with neratinib occurred in 421 of 924 total events in 11 trials [9-19], with incidence of high-grade events ranging from 10% to 78%. Overall incidence of high-grade diarrhea was 32.00% (95% CI 0.22-0.45), accor-

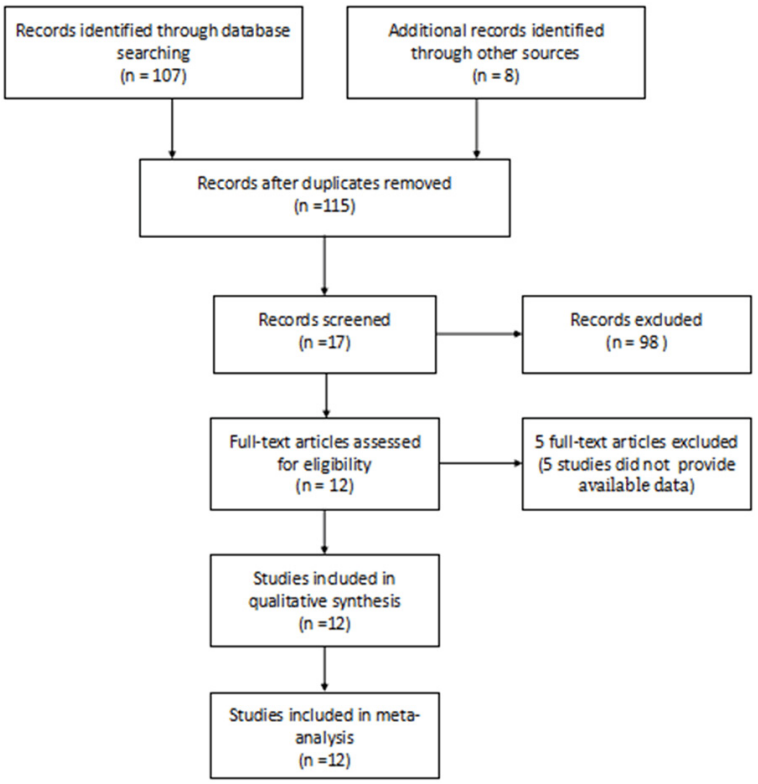

Figure 1. Flow diagram of the study selection process.

ding to the random-effects model meta-analysis ($P < 0.0001$; $I^2 = 90.9\%$) (**Figure 3A**).

Meta-analysis of RRs for diarrhea associated with neratinib was performed for the two RCTs [11, 14]. The heterogeneity of studies for analysis of all-grade events was not significant ($P = 0.15$; $I^2 = 51\%$). Blinded and open-label trials were examined, separately, to explore possible sources of heterogeneity in this study. Random-effects model analysis found that overall RR of all-grade diarrhea was 1.18 (95% CI 1.04-1.33) in patients with neratinib vs. controls [11, 14] (**Figure 4A**, **Table 3**). Regarding analysis of high-grade events, there was no significant interstudy heterogeneity ($P = 0.99$; $I^2 = 0\%$). For high-grade diarrhea, fixed-effects model meta-analysis gave an overall RR of 1.47(95% CI 1.07-2.00) for neratinib, compared with controls (**Figure 5A**).

Incidence of nausea

All 9 trials [10, 11, 13-17, 19, 20] reported all-grade nausea, occurring in 468 of 793 total events. Incidence of all-grade nausea ranged from 27% to 88% in patients assigned neratinib. Overall incidence of all-grade nausea was 60.00% (95% CI 0.48-0.70) in patients treated with neratinib, using a random-effects model ($P < 0.0001$; $I^2 = 88.9\%$) (**Figure 2B**). Random-effects model meta-analysis indicated that overall incidence of high-grade nausea was 8.00% (95% CI 0.03-0.21), which included 6 trials [10, 11, 14, 16, 18, 19] and 588 total events. Interstudy heterogeneity testing indicated that $P < 0.0001$; $I^2 = 92.6\%$ (**Figure 3B**).

Two trials [11, 14] were analyzed for RRs of all-grade nausea. Results showed a statistical increase in the risk of all-grade nausea [1.52 (95% CI 0.74-3.14)] using random-effects model meta-analysis ($P = 0.007$; $I^2 = 86.0\%$) for neratinib vs. controls (**Figure 4B**). For calculation of high-grade nausea, random-effects model ($P = 0.12$; $I^2 = 59\%$) comparison also revealed an increased risk of 2.53 (95% CI 0.83-7.70) (**Figure 5B**).

Incidence of vomiting

A total of 9 trials [10, 11, 13-17, 19, 20] (793 patients) were included for all-grade vomiting. Results of testing for interstudy heterogeneity showed that $P < 0.0001$; $I^2 = 89.70\%$, thus a random-effects model was used for meta-analysis. Overall incidence of all-grade vomiting was 43.00% (95% CI 0.31-0.56) in patients assigned neratinib (**Figure 2C**). All 6 trials [10-12, 16, 18, 19] reported high-grade vomiting, which occurred in 43 of 593 total events. As determined by the random-effects model ($P = 0.0023$; $I^2 = 76.5\%$), overall incidence of high-grade vomiting was 7.00% (95% CI 0.04-0.14) (**Figure 3C**).

Analysis of RRs of all-grade vomiting was carried out for two RCTs [11, 14] (367 patients). Results showed that use of neratinib significantly increased the risk of all-grade vomiting (1.47, 95% CI 1.07-2.00), according to the fixed-effects model ($P = 0.99$; $I^2 = 0$) (**Figure 4C**). In

Table 1. Summary of the characteristics of studies included in the meta-analysis

Trial	Trial design	Sample size, N	Region	Median age, years	Treatment	Histology	Quality score
Rachel C (2013) [9]	Phase I	21	USA	51 (35-64)	Neratinib 160 mg	Breast cancer	4
LW-C Chow (2013) [10]	Phase I/II (Neratinib vs. Paclitaxel)	102 (N)/8 (P)	UK	50.5 (20-76)	Neratinib 240 mg	Breast cancer	3
Miguel Martin (2014) [11]	Phase II (Neratinib vs. Capecitabin)	117 (N)/116 (C)	Spain	54 (30-79)	Neratinib 240 mg	Breast cancer	6
Cristina Saura (2014) [12]	Phase I/II (Neratinib vs. Lapatinib)	65 (N)/7 (L)	Spain	51 (33-79)	Neratinib 240 mg	Breast cancer	5
Awada (2012) [13]	Phase II (Neratinib vs. Vinorelbine)	64 (N)/37 (V)	Belgium	51.6 (40.8-62.4)	Neratinib 240 mg	Breast cancer	5
Harold J. Burstein (2012) [14]	Phase II (Neratinib vs. Trastuzumab)	70 (N)/60 (T)	USA	50 (31-83)	Neratinib 240 mg	Breast cancer	6
B. Besse (2008) [15]	Phase II	165	USA	60	Neratinib 240 mg	NSCLC	4
Lecia V. Sequist (2010) [16]	Phase II	167	USA	60 (22-86)	Neratinib 240 mg	NSCLC	4
Yoshinori Ito (2012) [17]	Phase I	21	Japan	61 (39-78)	Neratinib 240 mg	Solid Tumors (Breast, Colorectal, Gastric)	3
Leena Gandhi (2014) [18]	Phase I	60	USA	50.8	Neratinib 240 mg	Solid Tumors (Breast, NSCLC, Gastric)	4
Kwok-K. Wong (2009) [19]	Phase I	72	USA	57 (34-90)	Neratinib 240 mg	Solid Tumors (Breast, NSCLC, Gastric)	3
C Saura (2010) [20]	Phase I/II	15	UK	46 (37-69)	Neratinib 240 mg	Solid Tumors (Breast, NSCLC, Gastric)	4

Note N: Neratinib; P: Paclitaxel; C: Capecitabin; L: Lapatinib; V: Vinorelbine; T: Trastuzumab; NSCLC: Non-small-cell carcinoma.

Table 2. Meta-analysis of incidence of gastrointestinal events in cancer patients receiving neratinib

Program	Diarrhea		Nausea		Vomiting		Anorexia	
	All-grades	High-grade	All-grades	High-grade	All-grades	High-grade	All-grades	High-grade
Trials (n)	11	11	9	6	9	6	6	5
Patients (N)	993	924	793	588	793	593	612	447
Events	787	421	468	59	326	43	185	33
I^2	91.3%	90.9%	88.9%	92.6%	89.70%	76.5%	70.4%	85.6%
95% CI	0.78 (0.66-0.87)	0.40 (0.29-0.52)	0.6 (0.48-0.70)	0.08 (0.03-0.21)	0.43 (0.31-0.56)	0.07 (0.04-0.14)	0.31 (0.25-0.39)	0.07 (0.02-0.18)
P value	*P* < 0.0001	*P* < 0.0001	*P* < 0.0001	*P* < 0.0001	*P* < 0.0001	*P* = 0.0007	*P* = 0.0047	*P* < 0.0001

Table 3. Meta-analysis of the risk of gastrointestinal events in patients between neratinib and controls

Program	Diarrhea				Nausea				Vomiting				Anorexia			
	All-grades		High-grade		All-grades		High-grade		All-grades		High-grade		All-grades		High-grade	
Trials (n)	2		2		2		2		2		2		2		2	
Events/Patients (N)	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b
	164/182	139/185	64/182	45/185	86/182	61/185	35/182	12/185	64/182	45/185	67/247	45/192	39/182	9/185	24/182	1/185
I^2	51.00%		0.00%		86.00%		59.00%		0.00%		0.00%		0.00%		0.00%	
95% CI	1.18 (1.04-1.33)		1.47 (1.07-2.00)		1.52 (0.74-3.14)		2.53 (0.83-7.70)		1.47 (1.07-2.00)		1.45 (1.07-1.98)		4.47 (2.24-8.90)		16.93 (3.31-86.53)	
P value	*P* = 0.008		*P* = 0.02		*P* = 0.25		*P* = 0.10		*P* = 0.02		*P* = 0.02		*P* < 0.0001		*P* = 0.0007	

Note a: neratinib; b: controls.

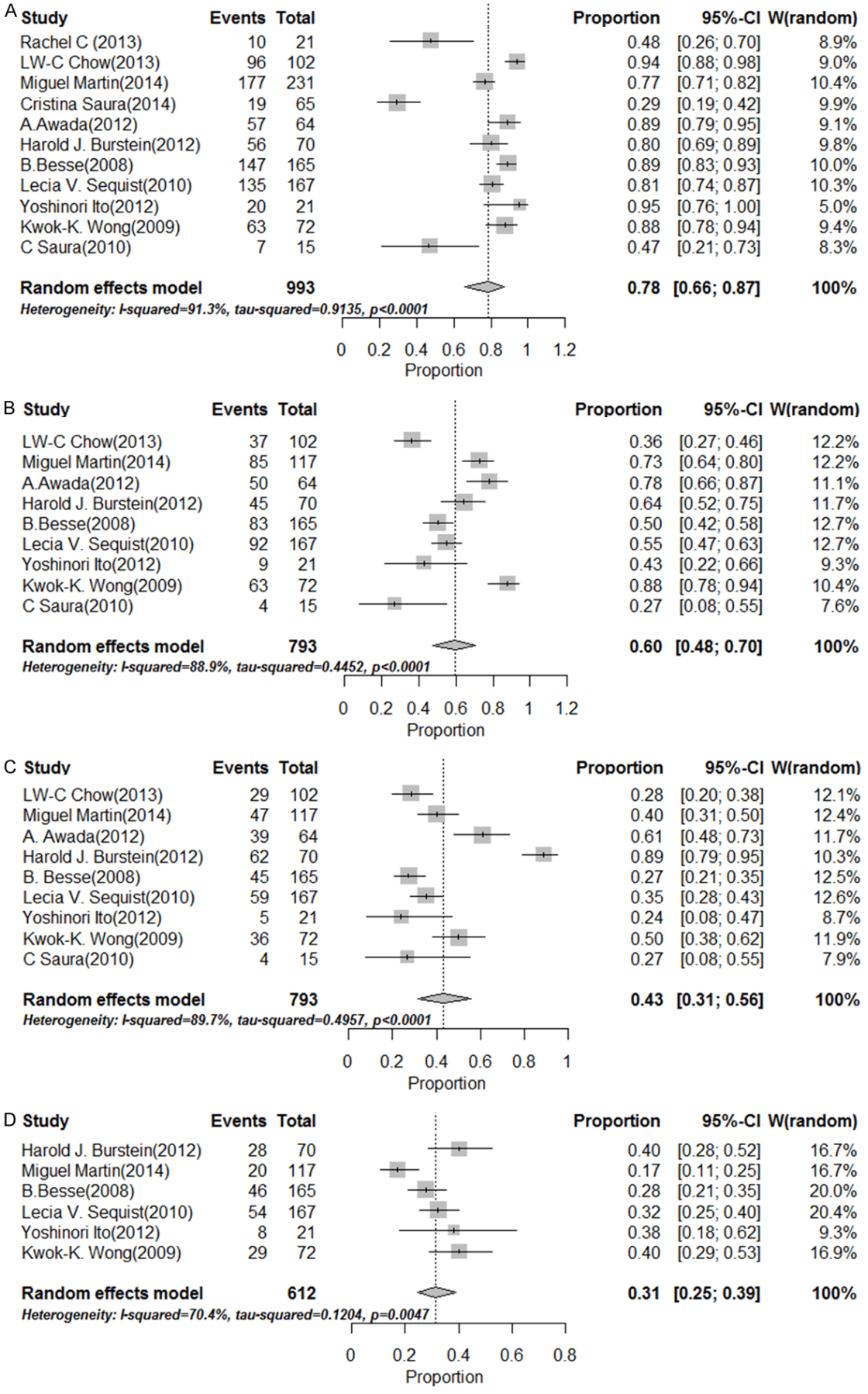
A
Study Events Total Proportion 95%-CI W(random)
Rachel C (2013) 10 21 0.48 [0.26; 0.70] 8.9%
LW-C Chow(2013) 96 102 0.94 [0.88; 0.98] 9.0%
Miguel Martin(2014) 177 231 0.77 [0.71; 0.82] 10.4%
Cristina Saura(2014) 19 65 0.29 [0.19; 0.42] 9.9%
A.Awada(2012) 57 64 0.89 [0.79; 0.95] 9.1%
Harold J. Burstein(2012) 56 70 0.80 [0.69; 0.89] 9.8%
B.Besse(2008) 147 165 0.89 [0.83; 0.93] 10.0%
Lecia V. Sequist(2010) 135 167 0.81 [0.74; 0.87] 10.3%
Yoshinori Ito(2012) 20 21 0.95 [0.76; 1.00] 5.0%
Kwok-K. Wong(2009) 63 72 0.88 [0.78; 0.94] 9.4%
C Saura(2010) 7 15 0.47 [0.21; 0.73] 8.3%
Random effects model 993 0.78 [0.66; 0.87] 100%
Heterogeneity: I-squared=91.3%, tau-squared=0.9135, p<0.0001
0 0.2 0.4 0.6 0.8 1 1.2
Proportion
B
Study Events Total Proportion 95%-CI W(random)
LW-C Chow(2013) 37 102 0.36 [0.27; 0.46] 12.2%
Miguel Martin(2014) 85 117 0.73 [0.64; 0.80] 12.2%
A.Awada(2012) 50 64 0.78 [0.66; 0.87] 11.1%
Harold J. Burstein(2012) 45 70 0.64 [0.52; 0.75] 11.7%
B.Besse(2008) 83 165 0.50 [0.42; 0.58] 12.7%
Lecia V. Sequist(2010) 92 167 0.55 [0.47; 0.63] 12.7%
Yoshinori Ito(2012) 9 21 0.43 [0.22; 0.66] 9.3%
Kwok-K. Wong(2009) 63 72 0.88 [0.78; 0.94] 10.4%
C Saura(2010) 4 15 0.27 [0.08; 0.55] 7.6%
Random effects model 793 0.60 [0.48; 0.70] 100%
Heterogeneity: I-squared=88.9%, tau-squared=0.4452, p<0.0001
0 0.2 0.4 0.6 0.8 1 1.2
Proportion
C
Study Events Total Proportion 95%-CI W(random)
LW-C Chow(2013) 29 102 0.28 [0.20; 0.38] 12.1%
Miguel Martin(2014) 47 117 0.40 [0.31; 0.50] 12.4%
A. Awada(2012) 39 64 0.61 [0.48; 0.73] 11.7%
Harold J. Burstein(2012) 62 70 0.89 [0.79; 0.95] 10.3%
B. Besse(2008) 45 165 0.27 [0.21; 0.35] 12.5%
Lecia V. Sequist(2010) 59 167 0.35 [0.28; 0.43] 12.6%
Yoshinori Ito(2012) 5 21 0.24 [0.08; 0.47] 8.7%
Kwok-K. Wong(2009) 36 72 0.50 [0.38; 0.62] 11.9%
C Saura(2010) 4 15 0.27 [0.08; 0.55] 7.9%
Random effects model 793 0.43 [0.31; 0.56] 100%
Heterogeneity: I-squared=89.7%, tau-squared=0.4957, p<0.0001
0 0.2 0.4 0.6 0.8 1
Proportion
D
Study Events Total Proportion 95%-CI W(random)
Harold J. Burstein(2012) 28 70 0.40 [0.28; 0.52] 16.7%
Miguel Martin(2014) 20 117 0.17 [0.11; 0.25] 16.7%
B.Besse(2008) 46 165 0.28 [0.21; 0.35] 20.0%
Lecia V. Sequist(2010) 54 167 0.32 [0.25; 0.40] 20.4%
Yoshinori Ito(2012) 8 21 0.38 [0.18; 0.62] 9.3%
Kwok-K. Wong(2009) 29 72 0.40 [0.29; 0.53] 16.9%
Random effects model 612 0.31 [0.25; 0.39] 100%
Heterogeneity: I-squared=70.4%, tau-squared=0.1204, p=0.0047
0 0.2 0.4 0.6 0.8
Proportion

Figure 2. Forest plot of the incidence of all-grade gastrointestinal events (A) diarrhea, (B) nausea, (C) vomiting, and (D) anorexia in cancer patients receiving neratinib.

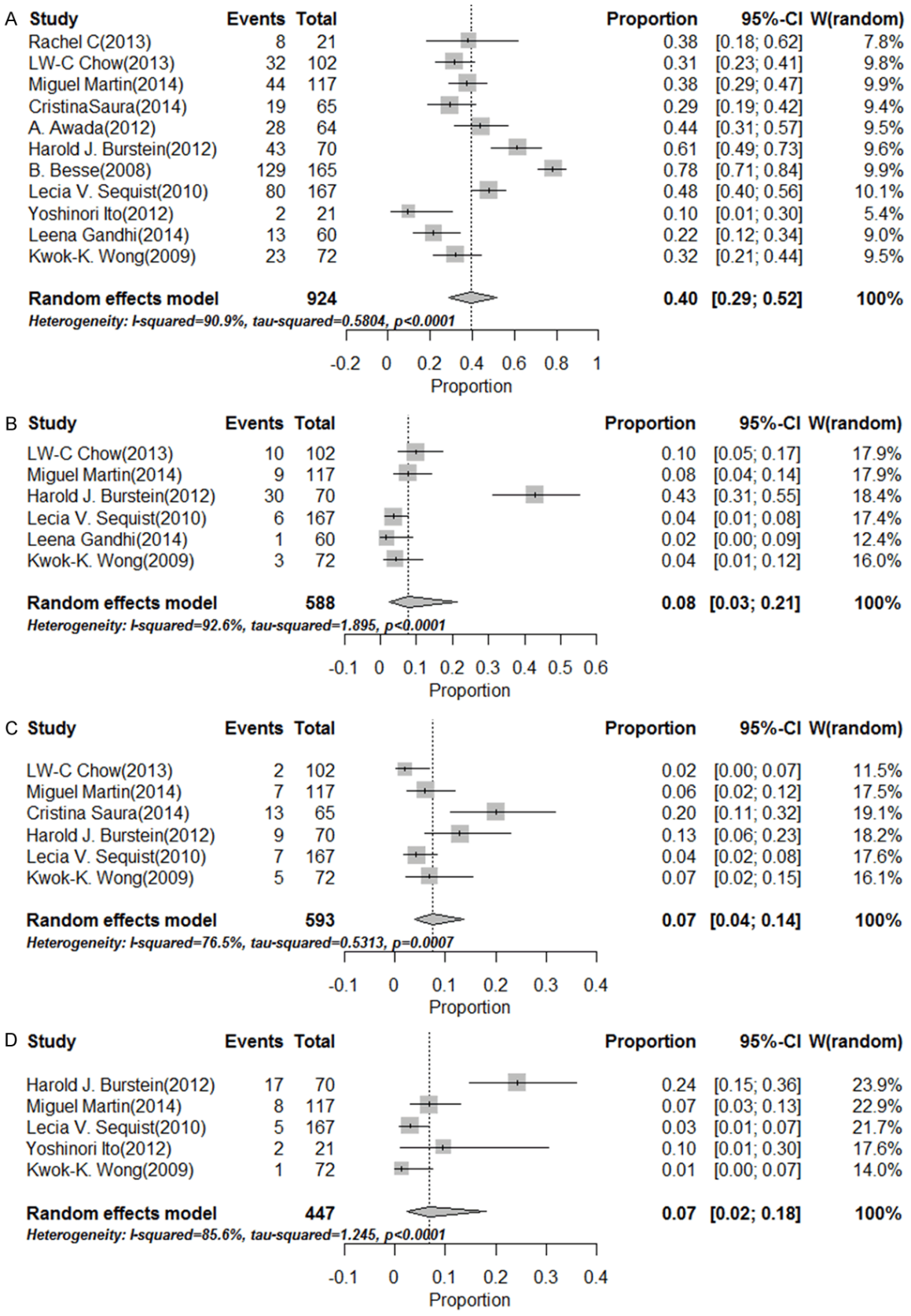

Figure 3. Forest plot of the incidence of high-grade gastrointestinal events (A) diarrhea, (B) nausea, (C) vomiting, (D) and anorexia in cancer patients receiving neratinib.

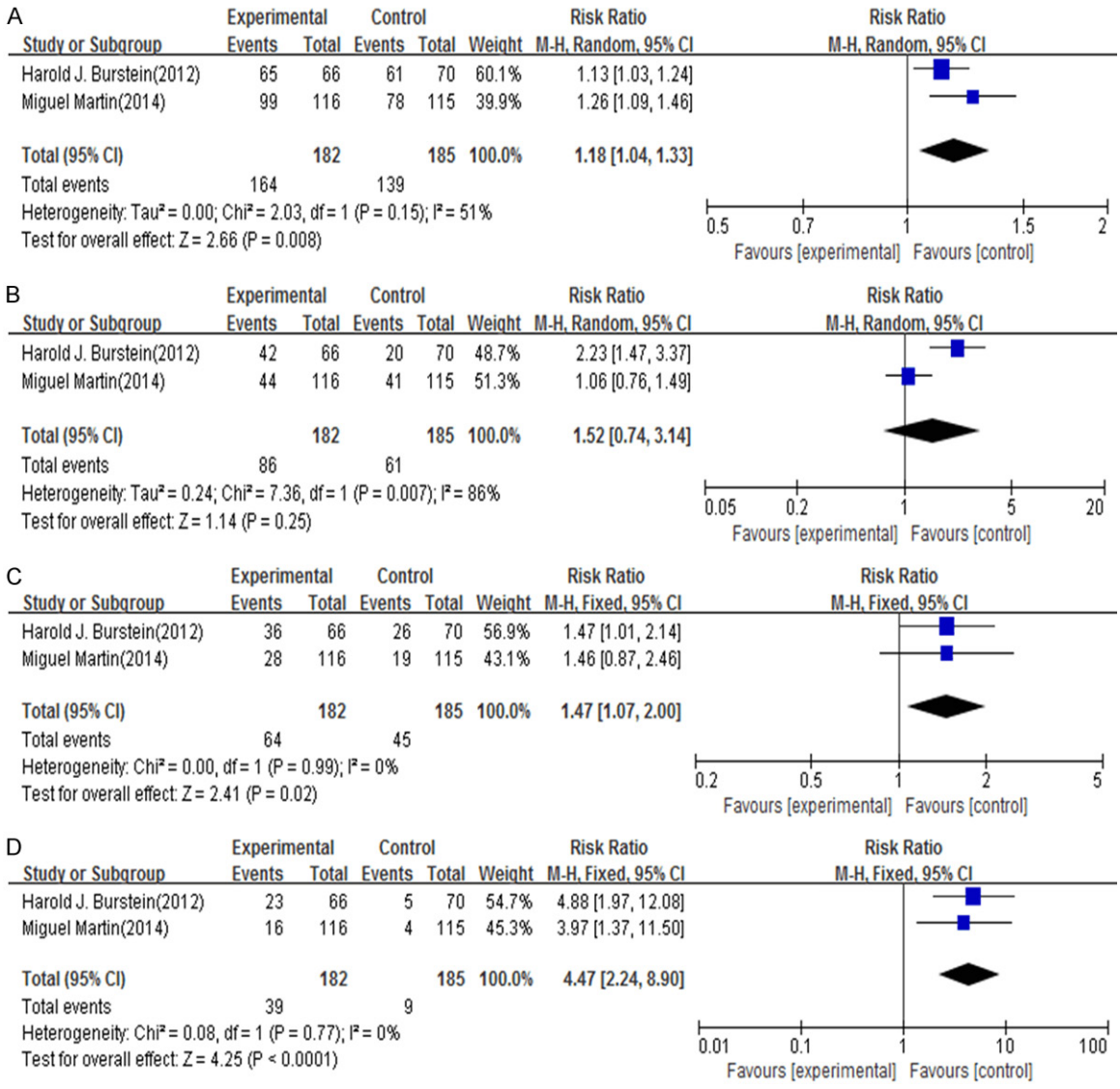

Figure 4. Forest plot of the RR of all-grade gastrointestinal events (A) diarrhea, (B) nausea, (C) vomiting, and (D) anorexia in cancer patients receiving neratinib.

addition, there were three RCTs [11, 12, 14] included in the meta-analysis with RRs of high-grade vomiting associated with neratinib. According to fixed-effects model meta-analysis ($P = 0.93$; $I^2 = 0$), RR of high-grade vomiting was 1.45 (95% CI 1.07-1.98) (**Figure 5C**).

Incidence of anorexia

A total of 6 trials [11, 14-17, 19] (612 patients) examined all-grade anorexia associated with neratinib treatment. Incidence ranged from 17% to 40%. Results of testing for interstudy heterogeneity showed that $P < 0.0001$; $I^2 = 89.1\%$, thus a random-effects model was used for meta-analysis. Overall incidence of all-grade anorexia was 31.00% (95% CI 0.25-0.39) in patients treated with neratinib (**Figure 2D**). All 5 trails [11, 14, 16, 17, 19], which occurred in 33 of 447 total events, were included in the meta-analysis for high-grade anorexia. Incidence of high-grade events ranged from 1% to 24%. Overall incidence of high-grade anorexia was 7.00% (95% CI 0.02-0.18), according to ran-

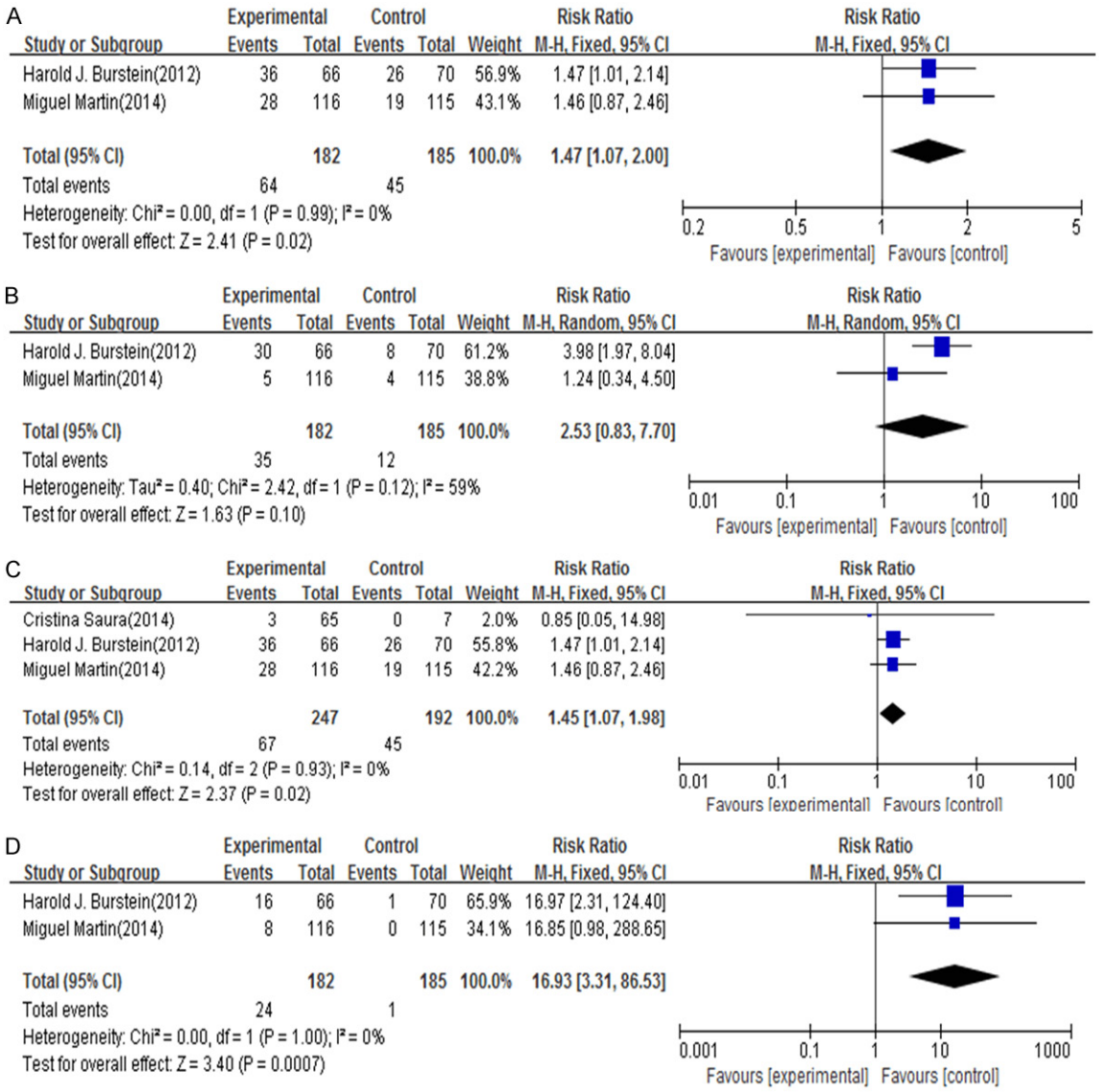

Figure 5. Forest plot of the RR of all-grade gastrointestinal events (A) diarrhea, (B) nausea, (C) vomiting, and (D) anorexia in cancer patients receiving neratinib.

dom-effects model meta-analysis (P = 0.0124; I^2 = 85.6%) (**Figure 3D**).

A meta-analysis of RRs of all-grade anorexia associated with neratinib, compared with controls, was performed on two trials [11, 14]. Using a fixed-effects model (heterogeneity test, I^2 = 0; P = 0.77), results showed that the summary RR of all-grade anorexia for neratinib vs. controls was 4.47 (95% CI, 2.24-8.90) (**Figure 4D**). High-grade anorexia was also investigated in the same trials [11, 14], with no significant interstudy heterogeneity (I^2 = 0; P = 1). The fixed-effects model comparison showed a significant risk for high-grade anorexia in patients with neratinib, compared with controls [RR: 16.93; 95% CI 3.3.1-86.53] (**Figure 5D**).

Publication bias

No evidence of publication bias was detected for incidence or RR of GI events (all and high grade), according to Begg's test and Egger's test (incidence: Begg's test, P = 0.47 and Egger's test, P = 0.29; RR: Begg's test, P = 0.30 and Egger's test, P= 0.51).

Discussion

To the best of our knowledge, this is the first meta-analysis focusing specifically on GI events

(diarrhea, nausea, vomiting, and anorexia) associated with neratinib [21, 22]. Results showed that diarrhea was the most frequently occurring gastrointestinal side-effect, with an overall incidence of 78.00% (95% CI 0.66-0.87) [23]. Results were consistent with previous research, demonstrating that neratinib or neratinib plus chemotherapy versus placebo or chemotherapy was associated with increased incidence of all-grade nausea in patients with cancer. The risk of nausea (all-grade: RR 3.51, 95% CI, 0.23-53.26 and high-grade: RR 7.34, 95%, 0.16-347.00) was not increased [24-26]. The risk of vomiting and anorexia was significantly higher for patients treated with neratinib, compared to the control group [27]. A phase 3 trial was performed to compare neratinib with lapatinib plus capecitabine in patients with treatment-naive advanced breast cancer [28]. It was found that both ORR (24%) and clinical benefit rates (29%) with lapatinib plus capecitabine were lower than rates seen with neratinib plus capecitabine. The most frequent all grade GI events were diarrhea (50%) and decreased appetite (29%) in the lapatinib group [29]. These studies confirm that neratinib plays a major role in all-grade and high-grade GI events in patients with cancer, suggesting that standard and careful management should be practiced for these side effects [30].

Association between GI toxicities and clinical outcomes in patients treated with neratinib still remains controversial. Diarrhea, one of the most common adverse events for patients treated with neratinib, can cause discomfort, fatigue, sleep disturbance, and can affect social function. However, very little is known about its mechanisms [31]. It has been reported that one reason may be local irritation by metabolites in the feces and transient lactose intolerance, a phenomenon occasionally seen with chemotherapy [32]. To explore the underlying mechanisms for neratinib-related GI events, further data from large clinical trials in other tumors are needed [33].

It is very import that receive nonpharmacological and pharmacological management for GI events associated with neratinib, because pain and discomfort of patients can be alleviated by adequate prevention and treatment [34]. First, it is advised that patients should realize the importance of managing GI events at the early treatment phase and avoid neratinib discontinuation. Second, the health care teams should be informed and ready to avoid hyponatremia or hypokalemia when GI events occur [35]. Third, GI protective agents, such as loperamide, omeprazole, and ondansetron, should be well be prepared before patients receive neratinib therapy. These agents should be immediately started at the onset of GI symptoms [36]. Fourth, for high-grade gastrointestinal events, treatment with neratinib should be terminated until GI events reach grade 1, after which neratinib should be dosed according to FDA recommendations [37].

The current meta-analysis had several limitations. First, because only 12 studies met the inclusion criteria, the small number of trials and low quality may have affected conclusions. Publication bias could not be completely excluded, based on Begg's and Egger's tests [38]. Second, researchers mostly adopted personal experience to diagnose gastrointestinal toxicities in the clinical trials. There were different judgements based on the same signs, varying between different researchers [39]. Third, this study was not able to correlate data with dose delays/interruptions or discontinuations secondary to GI adverse events. Fourth, study protocols and the process of research were different among studies included in this meta-analysis, possibly leading to significant heterogeneity in the data. Therefore, large-scale and well-designed studies are necessary to summarize and analyze the data, drawing more convincing conclusions [40].

Conclusion

In conclusion, the current study suggests that neratinib is associated with an increased risk of all-grade and high-grade GI toxicities. Other GI events occurring in patients need to be studied to confirm their relation to neratinib. The most frequently occurring GI event associated with cancer patients assigned with neratinib is diarrhea. Thus, physicians and patients should predict the risk of possible GI events associated with neratinib to the maximum extent, with frequent monitoring and careful management, aiming to improve patient outcomes and quality of life.

Disclosure of conflict of interest

None.

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