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Systematic Review

Cardiovascular Toxicity of Targeted Therapies for Cancer: An Overview of Systematic Reviews

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Abstract

Background: Several targeted therapies for cancer have been associated with cardiovascular toxicity. The evidence for this association has not been synthesized systematically nor has the quality of evidence been considered. We synthesized systematic review evidence of cardiovascular toxicity of individual targeted agents. **Methods:** We searched MEDLINE, Embase, and the Cochrane Database of Systematic Reviews for systematic reviews with meta-analyses of cardiovascular outcomes for individual agents published to May 2020. We selected reviews according to prespecified eligibility criteria (International Prospective Register of Systematic Reviews CRD42017080014). We classified evidence of cardiovascular toxicity as sufficient, probable, possible, or indeterminate for specific cardiovascular outcomes based on statistical significance, study quality, and size. **Results:** From 113 systematic reviews, we found at least probable systematic review evidence of cardiovascular toxicity for 18 agents, including high- and all-grade hypertension for bevacizumab, ramucirumab, axitinib, cediranib, pazopanib, sorafenib, sunitinib, vandetanib, aflibercept, abiraterone, and enzalutamide, and all-grade hypertension for nintedanib; high- and all-grade arterial thromboembolism (includes cardiac and/or cerebral events) for bevacizumab and abiraterone, high-grade arterial thromboembolism for trastuzumab, and all-grade arterial thromboembolism for sorafenib and tamoxifen; high- and all-grade venous thromboembolism (VTE) for lenalidomide and thalidomide, high-grade VTE for cetuximab and panitumumab, and all-grade VTE for bevacizumab; high- and all-grade left ventricular ejection fraction decline or congestive heart failure for bevacizumab and trastuzumab, and all-grade left ventricular ejection fraction decline/congestive heart failure for pazopanib and sunitinib; and all-grade corrected QT interval prolongation for vandetanib. **Conclusions:** Our review provides an accessible summary of the cardiovascular toxicity of targeted therapy to assist clinicians and patients when managing cardiovascular health.

Cancer treatment has changed dramatically over the past 2 decades with the evolution of more selective, mechanism-based therapies. Although these targeted therapies have contributed to considerable improvements in patient survival, they have been associated with short-term and longer term cardiovascular toxicity because of shared cardiovascular protein signaling pathways (1). These toxicities include but are not limited to hypertension, thromboembolism, reduction in left ventricular ejection fraction (LVEF), congestive heart failure, and arrythmias. Cardiovascular toxicity associated with established antineoplastic agents, such as anthracyclines, has been well described, whereas the evidence for targeted agents is still

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emerging. Moreover, and in contrast to anthracyclines, evidence-based guidelines for monitoring and managing potential cardiovascular toxicity in patients exposed to these agents are largely lacking (2,3).

Overviews of systematic reviews (also called umbrella reviews) collate information from multiple systematic reviews to provide a comprehensive synthesis of evidence (4,5). Additionally, they can provide a perspective on the heterogeneity, possible sources of bias, and methodological quality of systematic reviews that may affect the credibility of evidence in a field (6). There have been no systematically conducted overviews of the cardiovascular toxicity of targeted therapy for cancer. In this overview, we provide an accessible synthesis with which to inform clinicians in general practice, cardiology, and oncology, as well as patients, when managing cardiovascular health.

Methods

Protocol and Registration

Our study was conducted according to an a priori protocol (7) registered on the International Prospective Register of Systematic Reviews (PROSPERO CRD42017080014) (8,9). We followed methodological guidelines for overviews from the Cochrane Collaboration (4), the Joanna Briggs Institute (5), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (10,11).

Information Sources and Search Strategy

We searched MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. Our search strategy was based on predefined systematic review search filters (12) and was aided by an experienced research librarian. Search terms comprised keywords related to cancer, drug therapy, adverse events, toxicity, systematic reviews, and meta-analyses. The search strategy was adapted for each database (see Supplementary Methods). As per our published protocol, our initial search included English language studies published to December 31, 2016; we performed an updated search on May 20, 2020, to include studies published up to that date. We hand-searched reference lists to identify any further eligible studies. We used EndNote X8.0.1 (Thomson Reuters 2016) to manage retrieved studies.

Eligibility Criteria

We included published, peer-reviewed systematic reviews of phase II-III randomized controlled trials (RCTs) and observational cohort studies that reported meta- or pooled estimates for cardiovascular outcomes for individual targeted agents. Reviews in which the research question was not clearly defined, did not present the sources searched or a search strategy, or did not provide information on the inclusion and exclusion criteria applied were not considered systematic and were therefore not included (13). We also did not include systematic reviews published only in abstract form.

We included studies of human cancer patients, with no restrictions by cancer type, patient age, or sex. The definition of targeted therapy included agents within the World Health Organization Anatomical Therapeutic Chemical classification rubrics (14), as follows: monoclonal antibodies (L01XC), protein kinase inhibitors (L01XE), other antineoplastic agents (L01XX), hormone antagonists and related agents (L02B), and immunomodulating agents (L04AX). We included agents administered in both neoadjuvant and adjuvant settings, and restricted, where possible, to first-line therapy; we excluded studies solely examining second-line therapy because of the possibility of nonrandom distribution of patients with prior exposure. Exceptions were studies in metastatic prostate cancer patients, almost all of whom had received prior androgen deprivation therapy, and patients receiving extended adjuvant tamoxifen, our justification being equal distribution of prior exposure. We did not include photodynamic therapy.

To enable an assessment of individual agents, we included only those systematic reviews that compared the agent with placebo, or the agent in combination with standard therapy with standard therapy alone, with or without concurrent radiotherapy, surgery, or transplantation. We excluded systematic reviews with 1 or more studies in which the agent of interest was compared directly with another agent (head-to-head studies), network meta-analyses, or in which the agent was given in both the treatment and control arms. We included dose-specific estimates for bevacizumab (low or high, as specified by the study authors) where available; for studies presenting both dose-specific and "any dose" estimates, only the dose-specific estimates contributed to the evidence synthesis.

We included systematic reviews if they reported meta-estimates for at least 1 cardiovascular outcome. We considered all relevant diseases of the cardiovascular system, including but not limited to hypertension, arterial thrombosis (including myocardial infarction, ischaemic heart disease, and cerebrovascular disease), venous thrombosis (including deep vein thrombosis and pulmonary embolism), LVEF decline and congestive heart failure, and arrhythmia. Definitions of cardiovascular toxicity and grade were as reported by the study authors. We did not include hematological toxicities or edema.

Data Extraction

After initial duplicate removal, 2 reviewers (S.L. and C.V.) independently screened titles and abstracts against eligibility criteria. They retrieved potentially relevant studies in full-text format to further determine inclusion. The reviewers then extracted data from each included study independently using a predefined data extraction form, which was piloted and refined accordingly. Where data reported within systematic reviews were inconsistent, the reviewers contacted the authors directly for clarification; they excluded systematic reviews with data irregularities that could not be resolved by communication with the authors. The reviewers extracted the following data items: bibliographic details, methodological characteristics (study design and bias assessment, intervention, cardiovascular outcome), patient characteristics, and results. The reviewers resolved discrepancies through discussion and consultation with a third reviewer (M.v.L.) if consensus could not be reached.

Assessment of Methodological Quality of Included Reviews

Two reviewers (S.L. and C.V.) independently appraised the methodological quality of included reviews using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) (15,16), a validated and reliable tool (17). We did not exclude reviews based on their AMSTAR score; however, we used AMSTAR scores to preferentially select higher quality reviews in the case of overlapping primary studies (see "Evidence Synthesis").

Assessment of Quality of Evidence

Umbrella reviews should provide an indication of the quality of the primary studies underlying each of the systematic reviews that have been included in the umbrella reviews (5). However, there is no agreed-on method with which to evaluate the quality of evidence across systematic reviews (18). The GRADE system, as applied in Cochrane reviews (4), to assess the quality of evidence and strength of recommendations cannot be readily applied in overviews of systematic reviews (18,19). Given the scope of this overview, it was not feasible to judge the quality of each primary study included in each systematic review. Nevertheless, for each systematic review, we report in detail the method of bias assessment applied and the distribution of scores across each domain. Additionally, the strict criteria on which we based our synthesis ensured the contribution of only those systematic reviews in which the quality of primary studies was adequately reported and considered (see "Evidence Synthesis") (18).

Evidence Synthesis

We applied set criteria in the case of more than 1 systematic review of the same therapy in the same patient population and for the same cardiovascular outcome. If the primary studies were completely overlapping, we selected the review of the highest quality. If the primary studies were partially overlapping, we retained both reviews provided that the lower quality review added more than one-third new primary studies. And if the primary studies did not overlap, we retained both reviews. We noted systematic reviews that were removed because of completely overlapping primary studies and used footnotes to indicate systematic reviews with partially overlapping primary studies. For studies presenting meta-estimates for multiple organs, we selected only the all-organ estimate to avoid duplication with organ-specific studies.

We display the published meta-estimates for each agent and cardiovascular outcome; however, we did not compute an overview meta-estimate, because of marked heterogeneity in study populations and cardiovascular outcomes between studies and difficulty determining overlapping primary studies (20,21). We applied the criteria described in Figure 1 to classify agents as having sufficient, probable, or possible systematic review evidence of cardiovascular toxicity, indeterminate systematic review evidence of toxicity, or sufficient systematic review evidence of no toxicity for each cardiovascular outcome (7). This terminology is as per that applied by the International Association for Research on Cancer when synthesizing and classifying evidence regarding suspected hazards to human health (22). We considered evidence to be sufficient if a systematic review was of high quality, assessed the quality of the primary studies and took this into account in formulating their conclusions, and identified a statistically significant association based on at least 1000 exposed patients (23-25). We presented our evidence synthesis using a "stop-light indicator" for visualization (5). For each agent and cardiovascular outcome, evidence of cardiovascular toxicity superseded any other classification; where there was sufficient systematic review evidence of no cardiovascular toxicity, this superseded indeterminate evidence. We prepared a Plain Language Summary of our study according to the Cochrane standards (26).

Results

Eligible Systematic Reviews

We identified 22 113 nonduplicate, potentially relevant articles in our literature search (see Supplementary Figure 1, available online, for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram). After screening titles and abstracts, and full-text review, 160 systematic reviews were eligible for data extraction. We excluded a further 33 systematic reviews during the data extraction process, 18 due to the inclusion of primary studies containing head-to-head comparisons (27-44), 6 due to the inclusion of primary studies containing noncomparable or unclear trial arms (45-50), 5 due to the inclusion of primary studies of exclusively second-line therapies (51-55), and 4 due to unresolvable data irregularities or methodological issues (56-59). Due to overlapping primary studies in higher quality systematic reviews, 14 otherwise eligible systematic reviews did not contribute to the evidence synthesis (60-73). Our final evidence synthesis involved a total of 113 systematic reviews (74-186).

Characteristics of Included Systematic Reviews

Characteristics of the 113 systematic reviews that contribute to the evidence synthesis are given in Supplementary Table 1 (available online). Twenty-one (18.6%) systematic reviews were judged to be of high quality (AMSTAR score 8-11), 82 (72.6%) to be of moderate quality (AMSTAR score 4-7), and 10 (8.8%) to be of low quality (AMSTAR score 0–3). Less than one-half (n = 48, 42.5%) of systematic reviews assessed the quality of the primary studies and took this into account in formulating their conclusions. All but 3 (94,114,171) of the systematic reviews included RCTs only. There was heterogeneity by patient population, including by cancer site, type (predominantly solid), stage, and treatment setting. Only 22 (19.5%) of the systematic reviews were conducted exclusively in the first-line setting or presented subanalyses for the first-line setting.

There was also heterogeneity in the investigation and reporting of cardiovascular toxicity. Only 48 (42.5%) of included systematic reviews investigated adverse events, including cardiovascular toxicity, as a primary outcome. Approximately one-half (n = 60, 53.1%) used a version of the National Cancer Institute Common Toxicity Criteria for Adverse Events, the Common Toxicity Criteria, or the New York Heart Association Classification to define cardiovascular toxicity; the remainder did not report the source of the definition applied.

Systematic reviews often reported incomplete information about the contributing primary studies. For instance, length of follow-up either was mostly not reported (n = 63, 55.8%) or was incomplete (n = 33, 29.2%). Many systematic reviews (n = 20, 17.7%) did not report the number of exposed patients. Moreover, it was not always clear which primary studies contributed to which meta-estimate, complicating the assessment of overlapping primary studies.

Results of Evidence Synthesis

Meta-estimates were identified for 1 or more cardiovascular outcomes for 29 individual targeted agents, including 9 monoclonal antibodies, 12 protein kinase inhibitors, 2 "other antineoplastic agents," 5 hormone antagonists, and 2 immunomodulating agents. The evidence synthesis is

Classification[a]	Conditions
Sufficient systematic review evidence of toxicity	If the following were *all* met: 1) a statistically significant meta-estimate of effect (P < .05); 2) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met[b]; AND 3) the number of patients exposed to the agent was ≥1000.
Probable systematic review evidence of toxicity	If the following are *all* met: 1) a statistically significant meta-estimate of effect (P < .05); 2) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met[b]; AND 3) the number of patients exposed to the agent was <1000.
	If the following are *all* met: 1) a statistically significant meta-estimate of effect (P < .05); 2) the review was moderate quality (AMSTAR score 4-7), without satisfying AMSTAR elements 7 or 8[b], or of low quality (AMSTAR score ≤3); AND 3) the number of patients exposed to the agent was ≥1000.
Possible systematic review evidence of toxicity	If the following are *all* met: 1) a statistically significant meta-estimate of effect (P < .05); 2) review was either moderate quality (AMSTAR score 4-7), without satisfying AMSTAR elements 7 or 8[b], or low quality (AMSTAR score ≤3); AND 3) the number of patients exposed to the agent was <1000.
Sufficient systematic review evidence of no toxicity	If the following are *all* met: 1) a statistically nonsignificant meta-estimate of effect (P > .05); 2) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met[b]; AND 3) the number of patients exposed to the agent was ≥1000.
Indeterminate systematic review evidence of toxicity	If the following are *all* met: 1) a statistically nonsignificant meta-estimate of effect (P > .05); 2) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 & 8 were met[b]; AND 3) the number of patients exposed to the agent was <1000.
	If the following are *all* met: 1) a statistically nonsignificant meta-estimate of effect (P > .05); 2) the review was moderate quality (AMSTAR score 4-7), without satisfying both AMSTAR elements 7 and 8[b], or low quality (AMSTAR score ≤3); AND 3) the number of patients exposed to the agent was of any size.
	If the only study examining the cardiovascular outcome did not report the number of patients exposed to the agent, regardless of effect or study quality.

Figure 1. Classification used to synthesize evidence from systematic reviews of targeted agents and cardiovascular toxicity. Adapted by permission from BMJ Publishing Group Limited (van Leeuwen MT, Luu S, Gurney H, et al.) Cardiovascular toxicity of targeted therapies for cancer: a protocol for an overview of systematic reviews. *BMJ Open* 2018;8:e021064. doi : 10.1136/bmjopen-2017-021064.

[a]Classification color-coded as per the "stop-light indicator" applied to our evidence synthesis.

[b]AMSTAR elements 7 and 8: quality of included studies was assessed, documented, and used appropriately in formulating conclusions.

presented in Figure 2 and a Plain Language Summary in Supplementary Figure 2 (available online). Extracted meta-estimates for agents with at least probable systematic review evidence of cardiovascular toxicity are summarized in Tables 1-3; estimates are presented in full in Supplementary Tables 2-6 (available online).

There was sufficient evidence of (increased risk of) high-grade hypertension for bevacizumab, and at least probable evidence of all-grade hypertension, irrespective of dose (Table 1). There was sufficient evidence of high- and all-grade hypertension for pazopanib, sorafenib, aflibercept, abiraterone, and enzalutamide, and all-grade hypertension for vandetanib. There was probable evidence of high- and all-grade hypertension for axitinib, cediranib, and sunitinib; high-grade hypertension for vandetanib; and all-grade hypertension for nintedanib.

There was sufficient evidence of high- and all-grade thromboembolism and arterial thromboembolism, and high-grade cardiac events for any-dose bevacizumab (Table 2). There was sufficient evidence of high- and all-grade cardiac events for abiraterone, and high-grade cardiac events for trastuzumab. There was probable evidence of all-grade arterial thromboembolism and cardiac events for sorafenib. Conversely, there was sufficient evidence of no effect on high-grade thromboembolism for cetuximab in colorectal cancer patients, on high- or all-grade cardiac events for tamoxifen or enzalutamide, or on all-grade cardiac events for letrozole.

There was probable evidence of all-grade cerebrovascular events for high-dose bevacizumab. There was also probable evidence of all-grade cerebrovascular events for tamoxifen, but only for all settings combined; there was sufficient evidence of

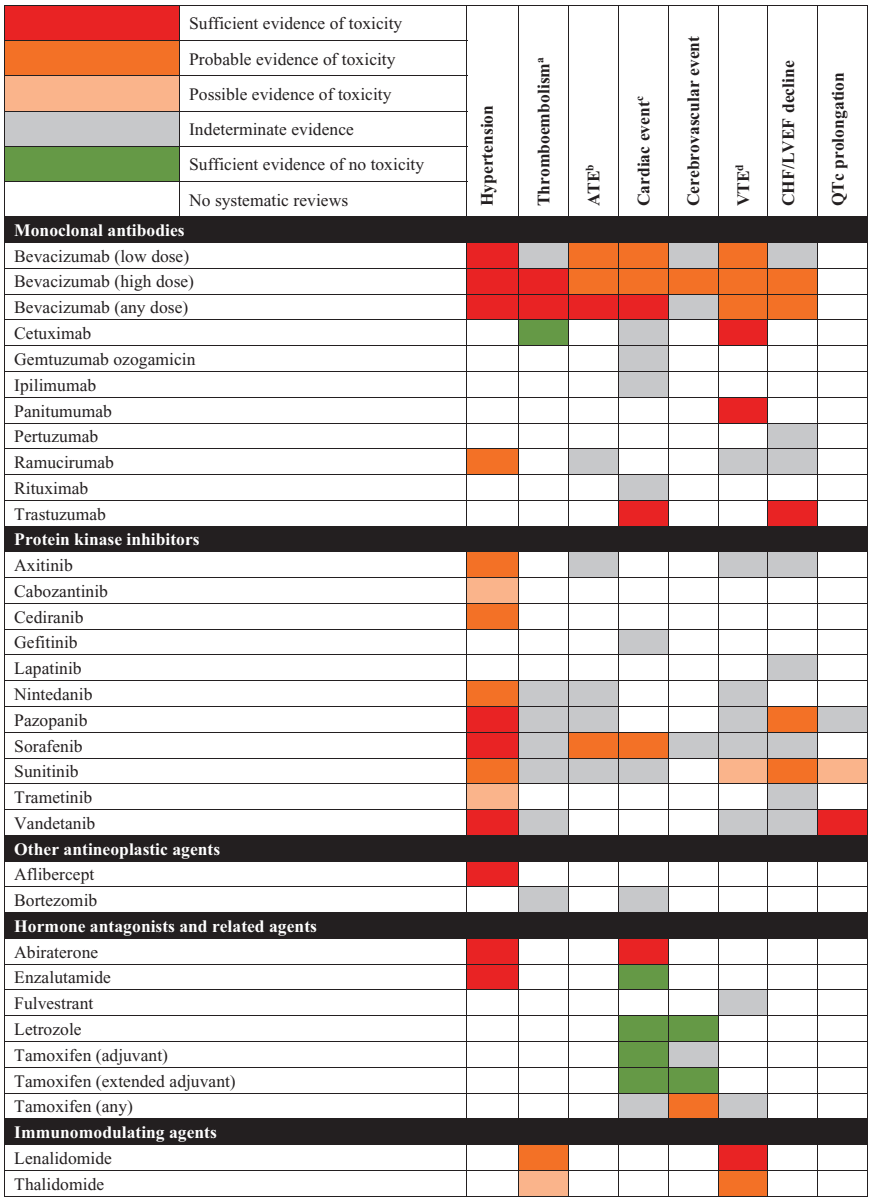

Figure 2. Synthesis of systematic review evidence of cardiovascular toxicity of targeted agents.

[a]Thromboembolism not otherwise specified or as defined by the study authors. May include arterial thromboembolism (ATE) and venous thromboembolism (VTE). CHF = congestive heart failure; LVEF = left ventricular ejection fraction; QTc = corrected QT.

[b]ATE not otherwise specified, or as defined by the study authors. May include cardiac, cerebrovascular, peripheral, and visceral arterial events.

[c]Cardiac event not otherwise specified, or as defined by the study authors. May include cardiac ischemia and myocardial infarction.

[d]VTE not otherwise specified, or as defined by the study authors. Also includes pulmonary embolism and deep vein thrombosis.

no effect of tamoxifen on cerebrovascular events in the extended adjuvant setting. There was sufficient evidence of no effect on all-grade cerebrovascular events for letrozole.

There was sufficient evidence of high-grade venous thromboembolism (VTE) for cetuximab and panitumumab and all-grade VTE for lenalidomide. There was probable evidence of high-grade VTE for both lenalidomide and thalidomide. There was probable evidence of all-grade VTE for bevacizumab, irrespective of dose, with the notable exception of bevacizumab studies in breast cancer patients, for which there was sufficient evidence of no effect.

There was sufficient evidence of high- and all-grade congestive heart failure or LVEF decline for trastuzumab and probable evidence for any-dose bevacizumab (Table 3). There was probable evidence of all-grade congestive heart failure or LVEF decline for pazopanib and sunitinib. There was sufficient evidence of all-grade QTc interval prolongation for vandetanib.

Discussion

We provide an overview of the cardiovascular toxicities of targeted therapy based on contemporary systematic review

Table 1. Summary of estimates for agents with at least probable systematic review evidence of hypertension

		High grade[a]				All grade[b]			
Agent	Molecular target	Highest level of evidence (ref)	Cancer	% Outcome in exposed[c]	RR or OR[d]	Highest level of evidence (ref)	Cancer	% Outcome in exposed[c]	RR or OR[d]
Bevacizumab, low dose	VEGF-A	Sufficient (141)	Solid	NR	4.8 (3.6 to 6.4)	Probable (178)	Solid	17.9	3.0 (2.3 to 3.8)
Bevacizumab, high dose	VEGF-A	Sufficient (141)	Solid	NR	5.4 (3.7 to 7.9)	Probable (156, 178)	Solid	Incomplete	4.1-7.1
Bevacizumab, any dose	VEGF-A	Sufficient (82, 94, 116, 117, 127, 162)	Solid	Incomplete	1.4-16.1	Sufficient (99, 141, 172)	Solid	Incomplete	3.0-5.1
Ramucirumab	VEGFR-2	Probable (145, 166)	Solid	9.0-9.9	3.7-4.2	Probable (145, 166)	Solid	19.6-21.2	2.7-3.6
Axitinib	VEGFR-1, -2, and -3	Probable (124)	Solid	6.0	4.2 (1.8 to 10.1)	Probable (157)	Solid	30.3	3.5 (2.0 to 6.2)
Cediranib	VEGFR-1, -2, and -3	Probable (124)	Solid	11.9	6.1 (3.4 to 11.0)	Probable (119, 124)	Solid	Incomplete	2.8-3.7
Nintedanib	VEGFR-2, FGFR-1, PDGFR-α and -β	—	—	—	—	Probable (157)	Solid	8.7	2.1 (1.10 to 4.17)
Pazopanib	VEGFR-1, -2, and -3; c-kit; PDGFR-α and -β; FGFR; c-Fms	Sufficient (124)	Solid	16.3	5.1 (3.6 to 7.2)	Sufficient (124)	Solid	47.0	7.6 (3.1 to 18.6)
Sorafenib	c-RAF; VEGFR-1, -2, and -3; PDGFR-β; c-kit; RET; FLT-3	Sufficient (124)	Solid	6.0	3.7 (2.9 to 4.6)	Sufficient (124)	Solid	14.4	3.1 (2.4 to 3.9)
Sunitinib	VEGFR-1, -2, and -3; PDGFR-α and β; c-kit; RET; FLT-3	Probable (119)	Solid	NR	4.1 (3.1 to 5.4)	Probable (119, 157)	Solid	Incomplete	4.4-5.0
Vandetanib	VEGFR-2, EGFR, RET	Probable (176)	Lung	1.6	3.1 (1.2 to 8.0)	Sufficient (169)	Lung	7.6	4.1 (2.5 to 6.6)
Aflibercept	VEGFR-1 and -2, PlGF	Sufficient (138)	Solid	13.8	5.0 (4.0 to 6.3)	Sufficient (138)	Solid	33.7	4.5 (3.8 to 5.2)
Abiraterone	CYP17A1	Sufficient (146)	mHSPC	13.6	2.3 (1.7 to 3.0)	Sufficient (180)	mCRPC	15.5	1.6 (1.3 to 1.9)
Enzalutamide	Androgen receptor	Sufficient (107, 183)	Prostate	Incomplete	2.1-2.7	Sufficient (107, 183)	Prostate	Incomplete	3.0-3.3

[a]As defined by systematic review study authors or where reported as grade 3 or greater (severe) based on National Cancer Institute Common Terminology Criteria for Adverse Events. — = no systematic reviews; CI = confidence interval; c-Fms = transmembrane glycoprotein receptor tyrosine kinase; c-kit = stem cell factor receptor; c-RAF = proto-oncogene serine/threonine-protein kinase; CYP17A1 = cytochrome P450 17A1; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; FLT-3 = FMS-like tyrosine kinase 3; mCRPC = metastatic castration resistant prostate cancer; mHSPC = metastatic hormone sensitive prostate cancer; NR = not reported; OR = odds ratio; PDGFR = platelet-derived growth factor receptors; PlGF = placental growth factor; RET = glial cell line-derived neurotrophic factor receptor (rearranged during transfection); RR = relative risk; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

[b]As defined by systematic review study authors or where grade was not specified.

[c]Shows range where evidence grade was informed by more than 1 study.

[d]Shows range in point estimates where evidence grade was informed by more than 1 study, or RR or OR (95% CI) where informed by 1 study.

Table 2. Summary of estimates for agents with at least probable systematic review evidence of thromboembolism

Outcome, agent	Molecular target	High-grade[a]				All-grade[b]			
		Highest level of evidence (ref)	Cancer	% Outcome in exposed[c]	RR or OR[d]	Highest level of evidence (ref)	Cancer	% Outcome in exposed[c]	RR or OR[d]
Thromboembolism									
Bevacizumab, high dose	VEGF-A	—	—	—	—	Sufficient (120)	Lung	—	1.8 (1.1 to 2.9)
Bevacizumab, any dose	VEGF-A	Sufficient (85, 127)	mCRC	7.0-7.9	1.6-1.8	Sufficient (82)	mCRC	12.1	1.4 (1.2 to 1.7)
Lenalidomide	Lymphoid transcription factors IKZF1 and IKZF3	Probable (165)	MM	8.5	3.4 (1.4 to 8.3)	—	—	—	—
ATE									
Bevacizumab, low dose	VEGF-A	Probable (148)	Solid	2.6	1.4 (1.0 to 2.0)	Probable (140)	Solid	NR	1.5 (1.1 to 2.1)
Bevacizumab, any dose	VEGF-A	Sufficient (161)	mCRC	2.9	2.1 (1.1 to 3.7)	Sufficient (116)	Ovarian	2.4	2.3 (1.3 to 4.0)
Sorafenib	c-RAF; VEGFR-1, -2, and -3; PDGFR-β; c-kit; RET; FLT-3	—	—	—	—	Probable (136)	Solid	1.7	2.3 (1.2 to 4.4)
Cardiac events									
Bevacizumab, low dose	VEGF-A	—	—	—	—	Probable (88)	Solid	1.9	2.1 (1.1 to 4.2)
Bevacizumab, high dose	VEGF-A	—	—	—	—	Probable (156)	Solid	1.6	4.4 (1.6 to 12.1)
Bevacizumab, any dose	VEGF-A	Sufficient (117)	Breast	1.7	3.2 (1.5 to 7.0)	—	—	—	—
Trastuzumab	HER-2	Sufficient (114, 160)	Breast	Incomplete	1.9-2.5	—	—	—	—
Sorafenib	c-RAF; VEGFR-1, -2, and -3; PDGFR-β; c-kit; RET; FLT-3	—	—	—	—	Probable (157)	Solid	1.5	2.0 (1.2 to 3.3)
Abiraterone	CYP17A1	Sufficient (144, 146)	mHSPC, mCRPC	4.0-6.5	2.1-2.9	Sufficient (180)	mCRPC	17.1	1.3 (1.0 to 1.6)
Cerebrovascular events									
Bevacizumab, high dose	VEGF-A	—	—	—	—	Probable (156, 186)	Solid	1.4-1.4	4.0-6.7
Tamoxifen[e]	ER-α and -β	—	—	—	—	Probable (83)	Breast	1.4	1.5 (1.1 to 2.0)
VTE									
Bevacizumab, low dose	VEGF-A	—	—	—	—	Probable (132)	Solid	NR	1.3 (1.1 to 1.6)
Bevacizumab, high dose	VEGF-A	—	—	—	—	Probable (132)	Solid	NR	1.3 (1.0 to 1.7)
Bevacizumab, any dose	VEGF-A	—	—	—	—	Probable (168)	Ovarian	NR	1.4 (1.0 to 2.0)

(continued)

Table 2. (continued)

Outcome, agent	Molecular target	High-grade[a]				All-grade[b]			
		Highest level of evidence (ref)	Cancer	% Outcome in exposed[c]	RR or OR[d]	Highest level of evidence (ref)	Cancer	% Outcome in exposed[c]	RR or OR[d]
Cetuximab	EGFR	Sufficient (130)	Solid	5.3	1.5 (1.2 to 1.8)	—	—	—	—
Panitumumab	EGFR	Sufficient (130)	Solid	9.0	1.5 (1.2 to 1.8)	—	—	—	—
Lenalidomide	Lymphoid transcription factors IKZF1 and IKZF3	Probable (185)	MM	4.4	2.6 (1.5 to 4.4)	Sufficient (170)	MM	6.1	2.5 (1.6 to 4.0)
Thalidomide	Lymphoid transcription factors IKZF1 and IKZF4	Probable (110)	MM	5.3	2.4 (1.2 to 5.1)	Probable (112)	MM	7.5	2.4 (1.1 to 5.5)

[a]As defined by systematic review study authors or where reported as grade 3 or greater (severe) based on National Cancer Institute Common Terminology Criteria for Adverse Events. — = no systematic reviews; CI = confidence interval; c-kit = stem cell factor receptor; c-RAF = proto-oncogene serine/threonine-protein kinase; CYP17A1 = cytochrome P450 17A1; EGFR = epidermal growth factor receptor; ER = estrogen receptor; FLT-3 = FMS-like tyrosine kinase 3; IKZF = Ikaros family zinc finger transcription factors; mCRC = metastatic colorectal cancer; mCRPC = metastatic castration resistant prostate cancer; mHSPC = metastatic hormone sensitive prostate cancer; MM = multiple myeloma; NR = not reported; OR = odds ratio; PDGFR = platelet-derived growth factor receptors; RET = glial cell line-derived neurotrophic factor receptor (rearranged during transfection); RR = relative risk; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

[b]As defined by systematic review study authors or where grade was not specified.

[c]Shows range where evidence grade was informed by more than 1 study.

[d]Shows range in point estimates where evidence grade was informed by more than 1 study, or RR or OR (95% CI) where informed by 1 study.

[e]Setting not specified.

Table 3. Summary of estimates for agents with at least probable systematic review evidence of CHF or LVEF decline and QTc interval prolongation

		High-grade[a]				All-grade[b]			
Outcome, agent	Molecular target	Highest level of evidence (ref)	Cancer	% outcome in exposed[c]	RR or OR[d]	Highest level of evidence (ref)	Cancer	% outcome in exposed[c]	RR or OR[d]
CHF or LVEF decline									
Bevacizumab, high dose	VEGF-A	Probable (92, 135)	Breast, solid	1.1-1.6	2.3-4.5	—	—	—	—
Bevacizumab, any dose	VEGF-A	Probable (93, 96, 167)	Breast, solid	Incomplete	2.3-5.7	Probable (143)	Breast	NR	3.4 (1.4 to 8.0)
Trastuzumab	HER-2	Sufficient (114, 131)	Breast	Incomplete	2.0-5.1	Sufficient (131)	Breast	11.2	1.8 (1.4 to 2.5)
Pazopanib	VEGFR-1, -2, and -3; c-kit; PDGFR-α and -β; FGFR; c-Fms	—	—	—	—	Probable (137)	Solid	5.9	2.4 (1.0 to 5.7)
Sunitinib	VEGFR-1, -2, and -3; PDGFR-α and β; c-kit; RET; FLT-3	—	—	—	—	Probable (157)	Solid	4.3	3.0 (1.9 to 4.5)
QTc interval prolongation									
Vandetanib	VEGFR-2, EGFR, RET	—	—	—	—	Sufficient (102, 155)	Lung, solid	2.8-6.3	9.6-13.0

[a]As defined by systematic review study authors, or where reported as grade 3 or higher (severe) based on National Cancer Institute Common Terminology Criteria for Adverse Events. — = no systematic reviews; CI = confidence interval; c-Fms = transmembrane glycoprotein receptor tyrosine kinase; CHF = congestive heart failure; c-kit = stem cell factor receptor; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; FLT-3 = FMS-like tyrosine kinase 3; LVEF = left ventricular ejection fraction; NR = not reported; OR = odds ratio; PDGFR = platelet-derived growth factor receptor; QTc = corrected QT; RET = glial cell line-derived neurotrophic factor receptor (rearranged during transfection); RR = relative risk; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.
[b]As defined by systematic review study authors or where grade was not specified.
[c]Shows range where evidence grade was informed by more than 1 study.
[d]Shows range in point estimates where evidence grade was informed by more than 1 study, or RR or OR (95% CI) where informed by 1 study.

evidence. We identified 113 eligible systematic reviews providing meta-estimates on cardiovascular toxicity for 29 individual targeted agents. We found at least probable systematic review evidence of cardiovascular toxicity for 18 agents, including: hypertension for bevacizumab, ramucirumab, axitinib, cediranib, nintedanib, pazopanib, sorafenib, sunitinib, vandetanib, aflibercept, abiraterone and enzalutamide; arterial (cardiac, cerebral) thromboembolism for bevacizumab, trastuzumab, sorafenib, abiraterone, and tamoxifen (selected settings); VTE for bevacizumab, cetuximab, panitumumab, lenalidomide, and thalidomide; LVEF decline or congestive heart failure for bevacizumab, trastuzumab, pazopanib, and sunitinib; and QTc interval prolongation for vandetanib.

The consistent evidence for increased risk of hypertension for bevacizumab, ramucirumab, several protein kinase inhibitors, as well as aflibercept relates to their mechanism of action on the vascular endothelial growth factor (VEGF) signalling pathway or its receptor (VEGFR). VEGF-VEGFR inhibitors interfere with nitric oxide–mediated vascular homeostasis, causing an imbalance between vasodilation and vasoconstriction; consequently, peripheral vascular resistance is increased, leading to hypertension (1). New-onset or worsening hypertension typically arises within the first few weeks of exposure (187) and is considered a marker of oncological efficacy (188). We did not identify any eligible systematic reviews of hypertension and regorafenib, because the primary studies were conducted solely in heterogenous, previously treated patients (124).

The increased risk of hypertension for men with metastatic castration-resistant and/or hormone-sensitive prostate cancer receiving enzalutamide and abiraterone is supported by recent observational data (189). Both therapies target the androgen signaling pathway: enzalutamide inhibits the androgen receptor, and abiraterone inhibits testosterone synthesis through inhibition of cytochrome P450 (CYP17A1) (190). Treatment with abiraterone can lead to increased levels of steroids with mineralocorticoid effects, including hypertension, mitigated by the use of prednisone (191). Most men had received prior androgen deprivation therapy, and some had received prior docetaxel. Observational data have consistently shown that androgen deprivation therapy in itself increases the risk of cardiovascular events (192) as well as metabolic syndrome and its components (hypertension, dyslipidaemia, hyperglycaemia, obesity) (193) because of the effect of inhibition of testosterone production on metabolic pathways.

The increased risk of arterial cardio- and cerebrovascular events for some monoclonal antibodies and protein kinase inhibitors relates to the disruption of endothelial cell function. Increased endothelial cell apoptosis results in exposure of the subendothelial membrane, activating the coagulation cascade and leading to thrombosis (194). Of interest, as noted by others, we saw increased risk of cardiovascular events for abiraterone but not enzalutamide, suggesting a different cardiovascular toxicity profile (73,107).

The conflicting evidence we observed for bevacizumab relates to heterogeneity in patient populations; there was increased risk in studies of patients with colorectal and solid tumors combined but not breast cancer. Patients may have different background risks of thrombosis—for instance, cardiovascular disease and colorectal cancer have shared risk factors—and different concurrent chemotherapy regimens.

We found sufficient evidence of no effect on arterial cardio- or cerebrovascular events in postmenopausal women with breast cancer receiving adjuvant or extended adjuvant tamoxifen; in fact, a 33% reduction in risk for cardiovascular events was reported for adjuvant tamoxifen (111). The potential cardioprotective effects of tamoxifen appear to relate to the alteration of serum lipid levels (195,196). We also saw no effect on cardio- or cerebrovascular events for extended adjuvant letrozole (111); previous evidence, largely based on head-to-head comparisons with tamoxifen, has been conflicting, possibly because of the cardioprotective effects of the latter (111,196,197). The effects of tamoxifen on venous thrombotic events were indeterminate (83), although evidence of increased risk is suggested by both RCT and observational data (197).

The increased risk of VTE, specifically deep vein thrombosis, in multiple myeloma patients treated with lenalidomide and thalidomide has been seen in both RCT and observational data and is consistently higher in patients concurrently treated with dexamethasone (198,199).

Cardiotoxicity in anthracycline-exposed patients receiving trastuzumab is well described; direct damage to myocytes by exposure to anthracyclines may render patients more vulnerable to trastuzumab-induced cardiotoxicity (200). We saw sufficient evidence of increased risk of LVEF decline and congestive heart failure in HER-2 positive breast cancer patients treated with trastuzumab with or following anthracycline treatment. In subanalyses, this effect was evident only for patients receiving anthracycline-containing regimens, not taxane- or aromatase inhibitor-containing regimens, although no statistically significant differences were detected due to small numbers (79).

There was sufficient evidence of increased risk of QTc interval prolongation in patients treated with vandetanib for various solid cancers; a dose-response effect has also been reported (102). Drug-induced QTc interval prolongation is caused by interaction with myocardial potassium ion channels (hERG K+) impeding electrical flow and delaying impulse conduction (201). This predisposes to malignant cardiac arrhythmias such as torsades de pointes and cardiac arrest.

Early detection and treatment of cardiovascular complications of cancer therapy is currently the primary focus of cardio-oncology (2,202). Our evidence synthesis supports recommendations for blood pressure monitoring and institution of early antihypertensive therapy for patients treated with agents targeting the VEGF-VEGFR signaling pathway, including bevacizumab, ramucirumab, axitinib, cediranib, nintedanib, pazopanib, sorafenib, sunitinib, vandetanib, and aflibercept as well as abiraterone and enzalutamide. Clinical surveillance for arterial or VTE is recommended for patients treated with bevacizumab, cetuximab, panitumumab, sorafenib, lenalidomide, and thalidomide. Cardiac surveillance by clinical review and noninvasive imaging is recommended for patients treated with bevacizumab, trastuzumab, pazopanib, sorafenib, sunitinib, vandetanib, and abiraterone.

Cardiovascular monitoring should be individualized based on patients' risk profile (202,203). Risk factors that predispose to cardiovascular toxicity should be discussed with patients, and modifiable risk factors should be addressed during and after cancer therapy. Monitoring with transthoracic echocardiogram and electrocardiogram should be considered in high-risk patients, such as those with preexisting cardiovascular disease or metabolic syndrome, prior chemotherapy or radiotherapy, or family history of cardiovascular disease (202). The detection of subclinical disease remains challenging, and recommendations for the routine use of biomarkers, such as troponin or brain natriuretic peptides, are not universal (2,3).

This is the first overview to our knowledge to appraise rigorously and synthesize comprehensively the published systematic review evidence of cardiovascular toxicity of targeted

therapy for cancer. Systematic reviews that adequately incorporate quality assessment are considered to provide the highest level of research evidence (204). The classification of sufficient or probable evidence of cardiovascular toxicity, or of no effect, was based only on high-quality reviews or on moderate-quality reviews in which the quality of primary studies was adequately assessed and also took the number of exposed patients into consideration. Our synthesis is therefore likely to be conservative. These steps were necessitated by the preponderance of low-quality systematic reviews, which fail to adequately account for the quality of primary studies (205).

Several limitations must be considered. Overviews of systematic reviews present several methodological challenges (18,20). First, our restriction to published systematic review evidence precludes the inclusion of agents for which systematic reviews have not yet been conducted or for which systematic reviews were deemed ineligible. Much of the eligible, published literature pertains to antiangiogenic agents; for instance, we found only 1 eligible systematic review on immune checkpoint inhibitors (108), and 1 on MEK inhibitors (74). Because there is currently no agreed method for the inclusion of additional primary studies, up-to-datedness remains an issue (206).

Second, despite our intention to include systematic reviews of observational studies, almost all were of RCTs. Estimates of cardiovascular risk based on RCTs may reflect outcomes in healthier populations, often without preexisting cardiovascular morbidity, and may therefore underestimate the toxicities that would be observed in routine clinical care. In addition, reporting of adverse events in RCTs is often suboptimal (207), and outcomes may be selectively included or reported in systematic reviews (208). Risk may also be underestimated because of insufficient follow-up time with which to observe late effects. The average length of follow-up for contributing primary studies was inadequately reported, and thus no conclusions can be drawn with respect to the timing of cardiovascular events.

Third, systematic review methodology was often poorly reported; a recent cross-sectional analysis of oncology systematic reviews found, for instance, that less than two-thirds are reproducible (209). The incomplete reporting of contributing primary studies complicated our assessment of overlapping primary studies, meaning that some primary studies may have been overrepresented. This, together with considerable heterogeneity in study populations, outcome definitions, and study quality, invalidated the computation of overview meta-estimates (20,21). Systematic reviews with overlapping primary studies are annotated in the tables and forest plots but nevertheless may give a false impression about the extent and consistency of the evidence; however, the stop-light indicator is unaffected by overlapping primary studies.

Fourth, in the absence of well-established criteria for classifying evidence, our approach has been guided by published umbrella reviews (23-25). Our use of cut points defined by the number of patients and statistical significance will have affected the classification for some agents. For instance, systematic reviews of cardiovascular outcomes involving less than 1000 exposed patients could only ever contribute probable evidence for that agent, regardless of study quality, statistical significance, or effect size.

We present a comprehensive summary and accessible reference table of the cardiovascular toxicity of targeted therapy for cancer based on current systematic review evidence. Our quality assessment ensures that our synthesis is based on the most robust studies. Guidelines for the management of cardiovascular toxicity associated with targeted therapy are lacking. Given the escalation of targeted therapy in contemporary practice, it is imperative that both clinicians and patients be provided with quality evidence with which to manage potential cardiovascular risk.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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