

Supporting Online Material

Chen WT, White CM, Phung OJ, Kluger J, Ashaye AO, Sobieraj DM, Makanji S, Tongbram V, Baker WL, Coleman CI. Association Between CHADS₂ Risk Factors and Anticoagulation-Related Bleeding: A Systematic Literature Review. *Mayo Clin Proc.* 2011;86(6):509-521

TABLE S1. Definitions for Grading the Strength of Evidence

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This supplementary material has been peer reviewed and the authors confirm that data are accurate.

Supporting Online Material

TABLE S1. Definitions for Grading the Strength of Evidence

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate
Very low	Very low confidence that the evidence reflects the true effect. Any estimate of effect is very uncertain
Insufficient	Evidence either is unavailable or does not permit estimation of an effect

TABLE S2. Evidence Depicting the Association Between Chronic Heart Failure and Warfarin-Associated Bleeding Risk^a

Reference	Study design	Covariate	Bleeding definition	No. of cases/events (rate/100 PTY)	Univariate <i>P</i> value	Multivariate “X”R (95% CI)	Multivariate <i>P</i> value	Effect (↑ ↔ ↓) ^b	Quality ^c
<i>Major bleeding event</i>									
Manzano-Fernández et al, ²¹ 2009 (N=166)	R, O	Previous heart failure (n=58)	A major bleeding event was defined as fatal decrease in blood Hgb level >4 g/dL (>40 g/L), need for transfusion of ≥2 units (≥900 mL) of blood, need for corrective surgery intervention, the occurrence of intracranial or retroperitoneal bleeding, or any combinations of these events	26 (10.8)	.442	NA	NA	NA	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of chronic heart failure (n=37)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	6 (NR)	.90	AOR, 2.5 (0.08-78.9)	.60	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of chronic heart failure (n=44)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	5 (NR)	.07	AOR, 1.1 (0.03-34)	.90	↔	Fair

Poli et al, ²³ 2007 (N=290)	P, O	LVSD defined as a recent diagnosis of heart failure or a fractional shortening <25% by transthoracic echocardiography (n=71)	Fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal, when surgery or transfusion of >2 blood units were required or when Hgb was reduced by ≥ 2 g/dL	17 (2.1)	NS	NA	NA	NA	Fair
Gasse et al, ¹⁸ 2005 (N=188)	R, O	Heart failure (n=85)	Bleeding events resulting in hospitalization or fatality	45 (NR)	0.05	AOR, 1.5 (0.7-3.2)	NS	\leftrightarrow	Fair
Schauer et al, ²⁵ 005a (N=9345)	R, O	Chronic heart failure (n=7140)	Inpatient hospitalization for ICH using <i>ICD-9-CM</i> codes	158 ^f (0.8)	NS	NA	NA	NA	Fair
Schauer et al, ²⁵ 2005b (N=9345)	R, O	Chronic heart failure (n=7140)	GI bleeding requiring hospitalization using <i>ICD-9-CM</i> codes	864 ^f (4.6)	<.05	AHR, 1.31 (1.09-1.58)	<.05	\uparrow	Fair
Fang et al, ¹⁷ 2004 (N=1190)	R, O	Heart failure (n=413)	ICH documented by computed tomography or magnetic resonance imaging	170 (NR)	.08	NA	NA	NA	Poor

Sam et al, ²⁴ 2004 (N=80)	R, O	Chronic heart failure (n=19)	Bleeding resulting in death, hospitalization, or a decrease in Hgb \geq 2 g/dL or requiring \geq 2 units of RBC transfusion	16 (NR)	NS	NA	NA	NA	Poor
Berwaerts & Webster, ¹⁶ 2000a (N=272)	R, O	Heart failure (n=101)	ICH	68 (NR)	NS	AOR, 1.02 (0.41-2.56) ^g	NS	\leftrightarrow	Fair
Berwaerts & Webster, ¹⁶ 2000b (N=168)	R, O	Heart failure (n=67)	Intracerebral hemorrhage	42 (NR)	NS	AOR, 0.72 (0.20–2.59) ^g	NS	\leftrightarrow	Fair
SPAF, 1996 (N=555)	RCT	Chronic heart failure (n=117)	A bleeding event was called major when it involved the central nervous system; required hospitalization, blood transfusion, and/or surgical intervention; or resulted in permanent functional impairment to any degree	33 ^f (2.3)	.05	NA	NA	NA	Poor
Hylek & Singer, ¹⁹ 1994a (N=308)	R, O	Chronic heart failure (n=54)	Intracerebral hemorrhage	77 (NR)	NS	NA	NA	NA	Poor

Hylek & Singer, ¹⁹ 1994 (N=176)	R, O	Chronic heart failure (n=40)	Subdural hemorrhage	44 (NR)	NS	NA	NA	NA	Poor
Landefeld & Foldman, ²⁰ 1989 (N=375) ^h	R, O	Heart failure (n=NR)	Bleeding in outpatients that (1) was fatal, (2) was life-threatening (led to cardiopulmonary arrest, surgical or angiographic intervention to stop the blood loss, or irreversible damage, such as MI, stroke, blindness, or fibrothorax), (3) was potentially life- threatening (led to 2 of 3 consequences: severe blood loss, hypotension (SBP <90 mm Hg), and critical anemia with a hematocrit ≤ 0.2), (4) led to severe blood loss (≥ 3 units of blood), (5) led to surgical treatment, or (6) led to moderate blood loss that was acute or subacute, and was not explained by	NR (NR)	NS	NA	NA	NA	Poor

trauma or surgery

Petitti et al, ²² 1989 (N=2029)	R, O	Treated heart failure (n=107)	Bleeding resulting in death or hospitalization	134 (NR)	<.05	AHR, 1.4 (0.9- 2.0)	NS	↔	Poor
Minor bleeding event									
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of chronic heart failure (n=37)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical consequences	47 (NR)	.90	AOR, 1.3 (0.40-4.0)	.70	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of chronic heart failure (n=44)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical consequences	42 (NR)	.60	AOR, 0.44 (0.16-1.2)	.10	↔	Fair

Petitti et al, ²² 1989 (N=2029)	R, O	Treated heart failure (n=107)	Bleeding not resulting in death or hospitalization	481 (NR)	NS	AHR, 0.6 (0.3- 0.9)	<.05	↓	Fair
<i>Any bleeding event</i>									
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of chronic heart failure (n=37)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	53 (NR)	.80	AOR, 1.1 (0.37-3.5)	.80	↔	Good

Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of chronic heart failure (n=44)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	47 (NR)	.90	AOR, 0.61 (0.24-1.6)	.30	↔	Fair
Wandell, ²⁶ 2001 (N=957)	R, O	Heart failure (n=NR)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospitalization; a minor bleeding event was defined as bleeding reported by patients and not requiring hospitalization	44 (6.2)	.01	NR	NS	↔	Poor

^a AHR = adjusted hazard ratio; AOR = adjusted odds ratio; CI = confidence interval; GI = gastrointestinal; Hgb = hemoglobin; *ICD-9-CM* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICH = intracranial hemorrhage; LVSD = left ventricular systolic dysfunction; MI = myocardial infarction; NA = not available; NR = not reported; NS = not significant; O = observational study; P = prospective; PTY = patient-years; R = retrospective; RBC = red blood cell; RCT = randomized controlled trial; SBP = systolic blood pressure; SPAF = Stroke

Prevention in Atrial Fibrillation; “X”R = effect size.

^b↑=statistically significant increased effect; ↓=statistically significant decreased effect; ↔=no statistically significant effect.

^c Quality rated as good, fair, or poor based on study design (prospective vs retrospective), likelihood of type 2 error (underpowered analysis due to insufficient patient-years of follow-up, small number of events, or too homogeneous a population), reliability of bleeding definition (use of a well-defined and accepted definition).

^d All patients in the group aged ≥ 75 y.

^e All patients in the group aged < 75 y.

^f Number of bleeding events reported.

^g Multivariate regression based on 50 cases of ICH and 200 controls because of incomplete data; 31 cases of intracerebral hemorrhage and 122 controls because of incomplete data.

^h Derivation cohort drawn from 565 patients beginning long-term outpatient warfarin therapy.

Table S3. Evidence Depicting the Association Between Hypertension and Warfarin-Associated Bleeding Risk^a

Reference	Study design	Covariate	Bleeding definition	No. of cases/ events (Rate/100 PTY)	Univariate <i>P</i> value	Multivariate “X”R (95% CI)	Multivariate <i>P</i> value	Effect (↑↔↓) ^b	Quality ^c
<i>Major bleeding event</i>									
Lind et al, ³¹ 2009a (N=356)	P, O	Hypertension (n=NR)	Major bleeding events were defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in Hgb level of ≥2 g/dL (≥20 g/L) or leading to transfusion of ≥2 units (≥900 mL) of whole blood	NR	NS	NA	NA	NA	Poor

Lind et al, ³¹ 2009b (N=356)	P, O	Hypertension (n=NR)	Clinically relevant bleeding was defined as a major bleeding event or an overt bleeding event based on objective investigations that caused admission to hospital or prolonged hospital care but did not meet the criteria for a major bleeding event	NR	NS	NA	NA	NA	Poor
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Manzano-Fernández et al, ²¹ 2009 (N=166)	R, O	Hypertension (n=108)	A major bleeding event was defined as fatal, decrease in blood Hgb level >4 g/dL (40 g/L), need for transfusion of ≥2 units of blood, need for corrective surgery intervention, the occurrence of intracranial or retroperitoneal bleeding, or any combinations of these events	26 (10.8)	.198	NA	NA	NA	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of hypertension (n=58)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	6 (NR)	.30	AOR, 4.5 (0.25-80.9)	.30	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of hypertension (n=55)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	5 (NR)	.70	AOR, 0.51 (0.01-25)	.70	↔	Fair

Poli et al, ²³ 2007 (N=290)	P, O	Hypertension defined as the presence of blood pressure >160 mm Hg and/or an anti-hypertensive treatment (n=177)	Fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal, when surgery or transfusion of >2 blood units were required or when Hgb was reduced by ≥ 2 g/dL (≥ 20 g/L)	17 (2.1)	NS	NA	NA	NA	Fair
Suzuki et al, ³⁴ 2007 (N=667)	R, O	Hypertension (n=527)	Bleeding requiring emergent hospitalization and ICHs	12 (2.4)	0.71	AOR, 1.32 (0.27-6.33)	NS	↔	Poor
Wallvik et al, ³⁵ 2007 (N=1579) ^f	P, O	Hypertension (n=523)	Bleeding event causing admission or prolonged in-hospital care and all fatal bleeding events	114 (NR)	NA	AOR, 1.06 (0.72-1.56)	NS	↔	Good

Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Hypertension (n=NR)	Hemorrhagic events were considered “serious” if the <i>ICD-9-CM</i> code was the primary diagnosis from a VA hospitalization	2546 ^g (1.9)	NR	AHR, 1.25 (1.13-1.38)	<.05	↑	Fair
Gasse et al, ¹⁸ 2005 (N=188)	R, O	Hypertension (n=81)	Bleeding events resulting in hospitalization or fatality	45 (NR)	.89	AOR, 0.9 (0.4-1.9)	NS	↔	Fair
Schauer et al, ²⁵ 2005a (N=9345)	R, O	Hypertension (n=7045)	Inpatient hospitalization for ICH using <i>ICD-9-CM</i> codes	158 ^d (0.8)	NS	NA	NA	NA	Fair
Schauer et al, ²⁵ 2005b (N=9345)	R, O	Hypertension (n=7045)	GI bleeding requiring hospitalization using <i>ICD-9-CM</i> codes	864 ^g (4.6)	NS	NA	NA	NA	Fair
Fang et al, ¹⁷ 2004 (N=1190)	R, O	Hypertension (n=740)	ICH documented by computed tomography or magnetic resonance imaging	170 (NR)	.10	NA	NA	NA	Poor

Sam et al, ²⁴ 2004 (N=80)	R, O	Hypertension defined according to JNC VII criteria (n=55)	Bleeding events resulting in death, hospitalization, or a decrease in Hgb ≥ 2 g/dL or requiring ≥ 2 units of RBC transfusion	16 (NR)	NS	NA	NA	NA	Poor
Berwaerts & Webster, ¹⁶ 2000a (N=272)	R, O	Hypertension (n=83)	ICH	68 (NR)	<.05	AOR, 2.69 (1.04-6.97) ^h	<.05	↑	Fair
Berwaerts & Webster, ¹⁶ 2000b (N=168)	R, O	Hypertension (n=58)	Intracerebral hemorrhage	42 (NR)	<.05	AOR 2.93 (0.87-9.87) ^h	NS	↔	Poor
McMahan et al, ³² 1998 (N=579)	R, O	Hypertension (n=304)	Bleeding event in outpatients that (1) was fatal, (2) was life-threatening (led to cardiopulmo- nary arrest, surgical or angiographic intervention to stop the blood loss, or irreversible damage, such as MI, stroke, blindness, or fibrothorax), (3) was potentially	40 ^g (5.9)	.68	NA	NA	NA	Poor

life-threatening
(led to 2 of 3
consequences:
severe blood
loss,
hypotension
(SBP <90 mm
Hg), and
critical anemia
with a
hematocrit of
.2), (4) led to
severe blood
loss (≥ 3 units of
blood), (5) led
to surgical
treatment, or
(6) led to
moderate blood
loss that was
acute or
subacute and
was not
explained by
trauma or
surgery

SPAF, 1996 (N=555)	RCT	Hypertension (n=289)	A bleeding event was called major when it involved the central nervous system; required hospitalization, blood transfusion, and/or surgical intervention; or resulted in permanent functional impairment to any degree	33 ^d (2.3)	NR	NR	NS	↔	Poor
Gitter et al, ³⁰ 1995 (N=261)	R, O	Hypertension (n=122)	Classified as a major bleeding event based on bleeding severity index determined independently by 2 physicians	18 (8.1)	NS	NR	NS	↔	Poor
Hylek & Singer, ¹⁹ 1994a (N=308)	R, O	Hypertension defined as documented in the medical record or use of antihyperten-sive agents (n=148)	Intracerebral hemorrhage	77 (NR)	NS	NA	NA	NA	Poor

Hylek & Singer, ¹⁹ 1994b (N=176)	R, O	Hypertension defined as documented in the medical record or use of antihypertensive agents (n=90)	Subdural hemorrhage	44 (NR)	NS	NA	NA	NA	Poor
Cortelazzo et al, ²⁸ 1993 (N=271)	R, O	Hypertension (n=11)	Hemorrhagic events requiring hospitalization documented by laboratory data: Hgb decrease of ≥ 2 g/dL	39 (2.7)	NS	NR	NS	\leftrightarrow	Poor

Fihn et al, ²⁹ 1993 (N=928)	R, O	Hypertension (n=NR)	Serious bleeding event was defined as a bleeding event requiring treatment or medical evaluation. Examples of serious bleeding included overt GIB, occult GIB if endoscopic or radiographic studies were done, gross hematuria that prompted cystoscopy or intravenous urography or lasted >2 d, and hemoptysis. If blood was transfused, ≤2 units were given	147 ^d (7.5)	NS	NA	NA	NA	Fair
Landefeld & Goldman, ²⁰ 1989 (N=375) ⁱ	R, O	Systolic blood pressure >140 mm Hg (n=54)	Bleeding in outpatients that (1) was fatal, (2) was life- threatening (led to cardiopul- monary arrest,	NR (NR)	<.05	NA	NA	NA	Poor

surgical or angiographic intervention to stop the blood loss, or irreversible damage, such as MI, stroke, blindness, or fibrothorax), (3) was potentially life-threatening (led to 2 of 3 consequences: severe blood loss, hypotension (SBP<90 mm Hg), and critical anemia with hematocrit ≤ 0.2), (4) led to severe blood loss (≥ 3 units of blood), (5) led to surgical treatment, or (6) led to moderate blood loss that was acute or subacute and was not explained by trauma or surgery

Petitti et al, ²² 1989 (N=2029)	R,O	Treated hypertension (n=380)	Bleeding resulting in death or hospitalization	134 (NR)	.05	AHR 1.4 (0.6- 2.5)	NS	↔	Fair
Minor bleeding event									
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of hypertension (n=58)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical conse- quences	47 (NR)	.001	AOR 3.3 (1.3- 8.1)	.01	↑	Good
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of hypertension (n=55)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical conse- quences	42 (NR)	0.008	AOR 2.3 (1.01- 5.4)	.06	↑	Good
Petitti et al, ²² 1989 (N=2029)	R, O	Treated hypertension (n=380)	Bleeding not resulting in death or hospitalization	481 (NR)	NS	AHR 1.0 (0.8- 1.3)	NS	↔	Fair
Any bleeding event									

Poli et al, ³³ 2009 (N=783)	P, O	History of hypertension and were taking antihypertensive treatment (n=495)	Combination of major and minor bleeding events where a major bleeding event was defined as fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; when surgery or transfusion >2 blood units were required or when Hgb was ≥ 2 g/dL; a minor bleeding event was defined as all cases of bleeding not categorized as major	94 (3.7)	.50	NA	NA	NA	Fair
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Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of hypertension (n=58)	Combination of major and minor bleeding where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	53 (NR)	<.001	AOR 3.6 (1.5-8.8)	.004	↑	Good
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Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of hypertension (n=55)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	47 (NR)	.01	AOR, 2.05 (0.91-4.6)	.08	↔	Fair
Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Hypertension (n=NR)	The presence of a hemorrhagic event was based on the presence of specific <i>ICD-9-CM</i> codes indicative of a bleeding event	10,249 ^g (7.7)	NR	AHR, 1.10 (1.05-1.16)	<.05	↑	Fair

Gitter et al, ³⁰ 1995 (N=261)	R, O	Hypertension (n=122)	Classified as major or minor bleeding event based on bleeding severity index determined independently by 2 physicians	27 (12.2)	NS	NR	NS	↔	Poor
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^a AHR = adjusted hazard ratio; AOR = adjusted odds ratio; CI = confidence interval; GI = gastrointestinal; GIB = GI bleeding; Hgb = hemoglobin;; *ICD-9-CM* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICH = intracranial hemorrhage; JNC = Joint National Committee; MI = myocardial infarction; NA = not available; NR =not reported; NS = not significant; O = observational study; P = prospective; PTY = patient-years; R = retrospective; RBC = red blood cell; RCT = randomized controlled trial; SBP = systolic blood pressure; SPAF = Stroke Prevention in Atrial Fibrillation; VA =Veterans Affairs; “X”R = effect size.

^b ↑=statistically significant increased effect; ↓=statistically significant decreased effect; ↔=no statistically significant effect.

^c Quality rated as good, fair, or poor based on study design (prospective vs retrospective), likelihood of type 2 error (underpowered analysis due to insufficient patient-years of follow-up, small number of events, or too homogeneous a population), reliability of bleeding definition (use of a well-defined and accepted definition).

^d All patients in the group aged ≥75 y.

^e All patients in the group aged <75 y.

^f Only Sundsvall subgroup used for multivariate regression.

^g Number of bleeding events reported.

^h Multivariate regression based on 50 cases of ICH and 200 controls because of incomplete data; 31 cases of intracerebral hemorrhage and 122 controls because of incomplete data.

ⁱ Derivation cohort drawn from 565 patients beginning long-term outpatient warfarin therapy.

TABLE S4. Evidence Depicting the Association Between Age and Warfarin-Associated Bleeding Risk^a

Reference	Study design	Covariate	Bleeding definition	No. of cases/ events (Rate/100 PTY)	Univariate <i>P</i> value	Multivariate “X”R (95% CI)	Multivariate <i>P</i> value	Effect (↑↔↓) ^b	Quality ^c
<i>Major bleeding event</i>									
Lind et al, ³¹ 2009a (N=719)	P, O	Linear age per decade (NA)	Major bleeding events were defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in Hgb level of ≥2 g/dL (≥20 g/L) or leading to transfusion of ≥2 units (≥900 mL) of whole blood	73 ^d (2.4)	<.05	AHR 1.36 (1.06–1.74)	<.05	↑	Good

Lind et al, ³¹ 2009b (N=719)	P, O	Linear age per decade (NA)	Clinically relevant bleeding was defined as a major bleeding event or an overt bleeding event based on objective investigations that caused admission to hospital or prolonged hospital care but did not meet the criteria for a major bleeding event	113 ^d (3.7)	<.05	AHR 1.45 (1.19–1.78)	<.05	↑	Good
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Manzano-Fernández et al, ²¹ 2009 (N=166)	R, O	Age >75 y (n=46)	A major bleeding event was defined as fatal, decrease in blood Hgb level >4 g/dL, need for transfusion of ≥2 units of blood, need for corrective surgery intervention, the occurrence of intracranial or retroperitoneal bleeding, or any combinations of these events	26 (10.8)	.049	AHR 2.75 (1.15–6.56)	.023	↑	Fair
Wallerstedt et al, ⁵⁴ 2009 (N=234)	R, O	Linear age per decade (NA)	Clinically relevant bleeding, defined as hospital admission due to bleeding	19 (2.4)	NA	AHR 0.62 (0.33–1.18)	.14	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^e	P, O	Linear age per year (NA)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	6 (NR)	.60	AOR 1.2 (0.87–1.7)	.30	↔	Fair

Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^f	P, O	Linear age per year (NA)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	5 (NR)	.60	AOR 1.3 (0.93–1.7)	.10	↔	Fair
Lindh et al, ⁴⁸ 2008 (N=1523)	P, O	Linear age per year (NA)	Severe bleedings were defined according to the WHO criteria; lethal, life-threatening, permanently disabling, or leading to hospital admission (emergency department admissions excluded) or prolongation of hospital stay and reviewed by 2 physicians	33 ^d (2.6)	NR	AHR 1.02 (0.98–1.06)	NS	↔	Good
Suzuki et al, ³⁴ 2007 (N=667)	R, O	Age ≥75 y (n=166)	Bleeding requiring emergent hospitalization and ICHs	12 (2.4)	0.49	AOR 1.66 (0.47–5.84)	NS	↔	Poor

Wallvik et al, ³⁵ 2007 (N=1579) ^g	P, O	Linear age per year (NA)	Bleeding event causing admission or prolonged in- hospital care and all fatal bleeding events	114 (NR)	NA	AOR 1.05 (1.03–1.08)	<.05	↑	Good
Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Age <55 y (n=NR) Age 55–64 y (n=NR) Age 65–74 y (n=NR) Age ≥75 y (n=NR)	Hemorrhagic events were considered ”serious” if the <i>ICD-9-CM</i> code was the primary diagnosis from a VA hospitalization	2546 ^d (1.9)	NR	Referent AHR 1.39 (1.14–1.69) AHR 1.47 (1.23–1.76) AHR 1.87 (1.56–2.24)	Referent <.05 <.05 <.05	NA ↑ ↑ ↑	Fair
Douketis et al, ³⁹ 2006 and Diener et al, ²⁸ 2006 (N=3665)	P, O	Age ≥75 y (n=1385)	Fatal bleeding; clinically overt bleeding associated with a reduction in Hgb level of ≥2 g/dL; clinically overt bleeding requiring transfusion of ≥2 units of whole blood or erythrocytes; intracerebral bleeding; and bleeding involving a critical anatomic site	136 (2.7)	NA	AHR 1.26 (1.03–1.52)	.02	↑	Good

			(intracranial [not intracerebral], intraspinal, intraocular, retroperitoneal, pericardial, or atraumatic intra-articular).						
Fang et al, ⁴⁰ 2006a (N=13,559)	P, O	Linear age per decade (NA)	Bleeding defined as fatal, requiring transfusion of ≥2 units packed blood cells, or hemorrhage into a critical anatomic site	170 (1.1)	<.05	ARR 1.2 (1.0-1.4)	≤.05	↑	Fair
Fang et al, ⁴⁰ 2006b (N=13,559)	P, O	Age ≥80 y (n=NR)	Intracranial hemorrhage	72 (0.5)	<.05	ARR 1.8 (1.1-3.1)	<.05	↑	Fair
Shireman et al, ³⁶ 2006 (N=19,875)	R, O	Age ≥70 y (n=17,490)	Bleeding defined as GI and intracranial hemorrhages that resulted in an inpatient admission, which were identified by diagnosis-related group codes and ICD-9CM codes, respectively	318 (NR)	NR	AHR, 1.63 (1.08-2.48)	<.05	↑	Fair

Schauer et al, ²⁵ 2005a (N=9345)	R, O	Linear age per decade (NA)	Inpatient hospitalization for ICH using <i>ICD-9-CM</i> codes	158 ^d (0.8)	NS	NA	NA	NA	Fair
Schauer et al, ²⁵ 2005b (N=9345)	R, O	Linear age per decade (NA)	GI bleeding requiring hospitalization using <i>ICD-9- CM</i> codes	864 ^d (4.6)	NS	NA	NA	NA	Poor
Fang et al, ¹⁷ 2004 (N=1190)	R,O	Linear age per 5 y (NA)	ICH documented by computed tomography or magnetic resonance imaging	170 (NR)	<0.001	AOR, 2.5 (1.3- 4.7) ^h	<.05	↑	Fair

Goudie et al, ⁴² 2004 (N=344)	Unclear	Linear age per decade (NA)	ICH (documented by imaging); surgery or angiographic intervention were required to stop bleeding; bleeding resulted in a reduction in Hgb levels of ≥2 g/dL or necessitated transfusion ≥2 units of blood; and when bleeding resulted in permanent loss of organ function (ie, intraocular bleeding causing blindness)	16 (2.4)	NA	AHR 1.25 (0.57-2.74)	.58	↔	Fair
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Kagansky et al, ⁴⁶ 2004 (N=323)	Combined P, O and R, O	Age \geq 90 y (n=NR)	Fatal, ocular (with blindness), articular, retroperitoneal, or if bleeding led to surgery, angiographic intervention, reduction of Hgb level of \geq 2 g/dL, or a need for a blood transfusion of \geq 2 packs	22 (3)	0.20	NR	NS	\leftrightarrow	Poor
Sam et al, ²⁴ 2004 (N=80)	R,O	Linear age per 5 y (NA)	Bleeding resulting in death, hospitalization, or a decrease in Hgb \geq 2 g/dL or requiring \geq 2 units of RBC transfusion	16 (NR)	NS	AOR, 1.10 (0.84-1.44)	.51	\leftrightarrow	Fair

Shireman et al, ⁵³ 2004 (N=10,093)	R, O	Linear age per year (NA)	Bleeding defined as GI and intracranial hemorrhages that resulted in an inpatient admission, which were identified by diagnosis-related group codes and <i>ICD-9-CM</i> codes, respectively	151 (NR)	<.05	AOR, 1.03 (1.00–1.05)	≤.05	↑	Fair
Kearon et al, ⁴⁷ 2003 (N=738)	RCT	Age ≥65 y (n=260)	Clinically overt bleeding resulting in a decrease in Hgb ≥2 g/dL, a need for ≥2 units of RBC transfusion, or involvement of a critical site	17 ^d (1)	NR	AHR, 2.6 (1.0-6.9)	≤.05	↑	Fair
Ruiz-Irastorza et al, ⁵¹ 2002 (N=66)	R, O	Linear age per year (NA)	Defined as intracranial, intraocular, GI, retroperitoneal, or requiring transfusion or admission to a hospital, were considered for the purposes of this study	4 (6)	NS	NR	NS	↔	Poor

Berwaerts & Webster, ¹⁶ 2000a (N=272)	R, O	Age ≥80 y (n=38)	ICH	68 (NR)	NS	AOR 1.46 (0.47-4.59) ⁱ	NS	↔	Poor
Berwaerts & Webster, ¹⁶ 2000b (N=168)	R, O	Age ≥80 y (n=26)	Intracerebral hemorrhage	42 (NR)	NS	AOR 1.38 (0.29-6.48) ⁱ	NS	↔	Poor
White et al, ⁵⁵ 1999 (N=21,250)	R, O	Age >65 y (n=NR)	Patients were categorized as having a hospital readmission for bleeding if the principal diagnosis was site-specific bleeding, system-specific bleeding, nonspecific hemorrhage, or prolonged blood clotting with a secondary diagnosis of a site- or system-specific bleeding code. A readmission was also included if the principal diagnosis was a potential source	298 (0.9)	NR	AHR 1.3 (1.0-1.7)	<.05	↑	Fair

			of bleeding with a secondary diagnosis bleeding.						
McMahan et al, ³² 1998 (N=579)	R, O	Age ≥65 y (n=340)	Bleeding in outpatients that (1) was fatal, (2) was life-threatening (led to cardiopulmonary arrest, surgical or angiographic intervention to stop the blood loss, or irreversible damage, such as MI, stroke, blindness, or fibrothorax), (3) was potentially life-threatening (led to 2 of 3 consequences: severe blood loss, hypotension (SBP <90 mm Hg), and critical anemia with a hematocrit ≤0.2), (4) led to severe blood	40 ^d (5.9)	0.93	AHR 1.0 (0.53–1.9) ^{j,k}	0.97	↔	Fair

			loss (≥ 3 units of blood), (5) led to surgical treatment, or (6) led to moderate blood loss that was acute or subacute, and was not explained by trauma or surgery.						
SPAF, 1996 (N=555)	RCT	Age >75 y (n=200)	A bleeding event was called major when it involved the central nervous system; required hospitalization, blood transfusion, and/or surgical intervention; or resulted in permanent functional impairment to any degree	33 ^d (2.3)	.009	NR	.006	↑	Good
Fihn et al, ⁴¹ 1996a (N=2300)	Combined R, O and P, O (82% of population)	Linear age per year (NA)	Fatal bleeding was defined as bleeding leading directly to the death of	37 (1)	NR	ARR 1.01 (0.99–1.04)	>.20	↔	Fair

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the patient.
Life-
threatening
bleeding was
defined as
bleeding
leading to
cardiopul-
monary arrest,
surgical or
angiographic
intervention, or
irreversible
sequelae, such
as MI,
neurologic
deficit
consequent to
intracerebral
hemorrhage, or
massive
hemothorax.
Bleeding was
also considered
to be life-
threatening if it
led to at ≤ 2 of
the following
consequences:
loss of ≥ 3 units
of blood;
systolic
hypotension
(SBP < 90 mm
Hg); or critical
anemia

			(hematocrit <0.2).						
Fihn et al, ⁴¹ 1996b (N=2300)	Combined R, O and P, O (82% of population enrolled prospectively)	Linear age per year (NA)	Serious bleeding was defined as bleeding requiring treatment or medical evaluation	222 (6.1)	NR	ARR, 0.99 (0.98-1.00)	.038	↔	Good
Gitter et al, ³⁰ 1995 (N=261)	R, O	Linear age per year (NA) ¹	Classified as a major bleeding event based on bleeding severity index determined independent-ly by 2 physicians	18 (8.1)	NS	AHR, 1.01 (0.98-1.05)	NS	↔	Fair
Gitter et al, ³⁰ 1995 (N=261)	R, O	Age <65 y (n=101) ¹ Age 65-74 y (n=78) ¹ Age ≥75 y (n=82) ¹	Classified as a major bleeding event based on bleeding severity index determined independent-ly by 2 physicians	18 (8.1)	Referent NS NS	NR	NS	↔	Fair
Hylek & Singer, ¹⁹ 1994a (N=308)	R, O	Linear age per decade (NA)	Intracerebral hemorrhage	77 (NR)	NR	AOR, 1.3 (1.0-1.6)	<.05	↑	Fair
Hylek & Singer, ¹⁹ 1994b (N=176)	R, O	Linear age per decade (NA)	Subdural hemorrhage	44 (NR)	NR	AOR, 2.0 (1.3-3.1)	.002	↑	Fair

Hylek & Singer, ¹⁹ 1994c (N=484)	R, O	Linear age per decade (NA)	Intracranial hemorrhage documented by computed tomography, lumbar puncture, or postmortem examination ^m	121 ⁿ (0.6)	NR	AOR, 1.4 (1.2-1.7)	<.001	↑	Fair
Cortelazzo et al, ²⁸ 1993 (N=271)	R, O	Age <40 y (n=48) Age 40–60 y (n=156) Age >60 y (n=67)	Hemorrhagic events requiring hospitalization documented by laboratory data: Hgb fall ≥2 g/dL	39 (2.7)	Referent NS NS	NR	NS	↔	Poor

Fihn et al, ²⁹ 1993 (N=928)	R, O	Age >65 y (n=NR)	Serious bleeding defined as bleeding requiring treatment or medical evaluation. Examples of serious bleeding included overt GIB, occult GIB if endoscopic, or radiographic studies were done, gross hematuria that prompted cystoscopy or intravenous urography or lasted >2 days, and hemoptysis. If blood was transfused, ≤2 units were given	147 ^d (7.5)	<.05	AHR, 0.80 (0.54-1.02)	>.20	↔	Fair
Landefeld & Goldman, ²⁰ 1989 (N=375) ^o	R, O	Age ≥65 y (n=172)	Bleeding in outpatients that (1) was fatal, (2) was life- threatening (led to cardiopul-	NR (NR)	<.001	AHR, 1.03 (NR)	<.01	↑	Fair

monary arrest,
surgical or
angiographic
intervention to
stop the blood
loss, or
irreversible
damage, such
as MI, stroke,
blindness, or
fibrothorax),
(3) was
potentially life-
threatening (led
to 2 of 3 conse-
quences: severe
blood loss,
hypotension
(SBP <90 mm
Hg), and
critical anemia
with a
hematocrit
≤0.2), (4) led to
severe blood
loss (≥3 units
of blood), (5)
led to surgical
treatment, or
(6) led to
moderate blood
loss that was
acute or
subacute, and
was not
explained by

			trauma or surgery.						
Petitti et al, ²² 1989 (N=2029)	R, O	Age ≥75 y (n=137)	Bleeding resulting in death or hospitalization	134 (NR)	NS	NA	NA	NA	Poor
Gurwitz et al, ⁴⁴ 1988 (N=321)	R, O	Age <50 y (n=73) Age 50–59 y (n=58) Age 60–69 y (n=104) Age ≥70 y (n=86)	Bleeding requiring hospitalization, transfusion, or discontinuation of warfarin therapy	14 (NR)	NS	NR	NS	↔	Poor
<i>Minor bleeding event</i>									
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^e	P, O	Linear age per year (NA)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical consequences	47 (NR)	.20	AOR, 0.95 (0.85-1.1)	.40	↔	Good

Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^f	P, O	Linear age per year (NA)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical consequences	42 (NR)	.20	AOR, 1.0 (0.95-1.1)	.90	↔	Good
Goudie et al, ⁴² 2004 (N=344)	Unclear	Linear age per decade (NA)	Bleeding events resulting in hospitalization for assessment or treatment, except ICH, requiring surgery or angiographic intervention to stop bleeding, reduction in Hgb ≥ 2 g/dL, or necessitated transfusion ≥ 2 units of blood, and bleeding resulting in permanent loss of organ function	27 (4.1)	NA	AHR, 1.28 (0.83-1.96)	.27	↔	Fair

Kagansky et al, ⁴⁶ 2004 (N=323)	Combined P, O and R, O	Age ≥90 y (n=NR)	All cases of bleeding except bleeding that is fatal, ocular (with blindness), articular, retroperitoneal, or if bleeding led to surgery, angiographic intervention, reduction of Hgb level of ≥2 g/dL, or a need for a blood transfusion of ≥2 packs	20 (2.7)	.60	NR	NS	↔	Poor
Fihn et al, ⁴¹ 1996 (N=2,300)	Combined R, O and P, O (82% of population enrolled prospectively)	Linear age per year (NA)	Bleeding with no associated costs or medical consequences	553 (21.8)	NR	ARR, 1.01 (1.00-1.02)	.001	↑	Good
Petitti et al, ²² 1989 (N=2,029)	R, O	Age ≥75 y (n=137)	Bleeding not resulting in death or hospitalization	481 (NR)	NS	NA	NA	NA	Poor

Gurwitz et al, ⁴⁴ 1988 (N=321)	R, O	Age <50 y (n=73) Age 50–59 y (n=58) Age 60–69 y (n=104) Age ≥70 y (n=86)	Bleeding events not requiring hospitaliza- tion, transfusion, or discontinua- tion of warfarin therapy	61 (NR)	NS	NR	NS	↔	Poor
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*Any bleeding
event*

Poli et al, ³³ 2009 (N=783)	P, O	Age ≥80 y (n=456)	Combination of major and minor bleeding events where a major bleeding event was defined as fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; when surgery or transfusion >2 blood units were required or when Hgb was ≥2 g/dL; a minor bleeding event was defined as all cases of bleeding not categorized as major	94 (3.7)	.002	AOR, 2.0 (1.1-4.0)	.05	↑	Fair
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Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^e	P, O	Linear age per year (NA)	Combination of major and minor bleeding events where a major bleeding event was defined as a bleeding event requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	53 (NR)	0.1	AOR, 0.97 (0.88-1.1)	0.6	↔	Good
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Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^f	P, O	Linear age per year (NA)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	47 (NR)	.10	AOR, 1.0 (0.96-1.1)	.80	↔	Good
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Metlay et al, ⁴⁹ 2008 (N=2346)	P, O	Age <70 y (n=283)	Warfarin- related	111 ^d (4.7)	Referent NS	Referent AIRR, 0.69 (0.31-1.51)	Referent NS	NA ↔	Fair
		Age 71-75 y (n=539)	bleeding, defined as any		NS	AIRR, 1.09 (0.52-2.26)	NS	↔	
		Age 76-80 y (n=663)	hospitalization with clinical		NS	AIRR, 1.61 (0.78-3.32)	NS	↔	
		Age 81-85 y (n=577)	signs and symptoms of			AIRR, 1.13 (0.43-2.94)			
		Age ≥86 y (n=285)	bleeding with evidence of elevated INR upon admission, a physician's attribution in the discharge summary of the hospitalization as due to warfarin toxicity, or evidence of administration of vitamin K or fresh frozen plasma						

Shalansky et al, ⁵² 2007 (N=171)	P, O	Linear age per year (NA)	Bleeding events based on patients' self-assessment, using a checklist of bleeding event types: excessive bruising beyond what the patient typically experiences while taking warfarin, excessive bleeding from a cut, nosebleed, blood in urine, blood in stool, blood in vomit, or other	359 ^d (NR) (87 patients reported ≥1 bleeding event)	NR	AOR, 1.03 (1.001.06)	.04	↑	Fair
Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Age <55 y (n=NR) Age 55-64 y (n=NR) Age 65-74 y (n=NR) Age ≥75 y (n=NR)	The presence of a hemorrhagic event was based on the presence of specific ICD-9-CM codes indicative of a bleed	10,249 (7.7)	NR	Referent AHR, 1.18 (1.07-1.29) AHR, 1.24 (1.14-1.35) AHR, 1.35 (1.24-1.47)	Referent <.05 <.05 <.05	NA ↑ ↑ ↑	Fair

Bini et al, ³⁷ 2005 (N=210)	P, O	Age 50-59 y (n=NR) Age 60-69 y (n=NR) Age 70-79 y (n=NR) Age ≥80 y (n=NR)	Fecal occult blood test positive with lesions that were considered to be a potential source of occult GIB loss were defined prior to the start of the study and similar to criteria used in other published studies	124 ^d (11.8)	Referent .23 .21 .01	Referent NA NA NR	Referent NA NA NS	↔	Poor
Ogendo, ⁵⁰ 2001 (N=150)	Combined R, O and P, O	Linear age per year (NA)	No definition provided	31 ^d (4.2)	NR	AOR, 0.97 (NR)	NS	↔	Poor
Gulløv et al, ⁴³ 1998, 1999 (N=170)	P, O	Linear age per year (NA)	Any bleeding complication	46 (13)	NA	NR	NS	↔	Fair
Gitter et al, ³⁰ 1995 (N=261)	R, O	Linear age per year (NA) ^l	Classified as major or minor bleeding event based on bleeding severity index determined independently by 2 physicians	27 (12.2)	NS	AHR, 1.00 (0.98-1.03)	NS	↔	Poor

Gitter et al, ³⁰ 1995 (N=261)	R, O	Age <65 y (n=101) [↓] Age 65–74 r (n=78) [↓] Age ≥75 r (n=82) [↓]	Classified as major or minor bleeding event based on bleeding severity index determined independently by 2 physicians	27 (12.2)	Referent NS NS	NR	NS	↔	Poor
Isaacs et al, ⁴⁵ 1994 (N=215)	R, O	Age 55–64 y (n=20) ^P Age 65–74 y (n=37) Age 75–84 y (n=95) Age ≥85 y (n=63)	Bleeding complication defined as any clinically visible evidence of bleeding, such as from a respiratory site, microscopic or macroscopic hematuria, major or minor GI bleeding, or an unusually large hematoma as recorded in the progress notes	27 (NR)	NS	NR	NS	↔	Poor

^a AHR = adjusted hazard ratio; AIRR = adjusted incidence rate ratio; AOR = adjusted odds ratio; ARR = adjusted relative risk; CI = confidence interval; GI = gastrointestinal; GIB = GI bleeding; Hgb = hemoglobin; *ICD-9-CM* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICH = intracranial hemorrhage; INR = International normalized ratio; MI = myocardial infarction; NA = not available; NR = not reported; NS = not significant; O = observational study; P = prospective; PTY = patient-years; R = retrospective; RBC = red blood cell; RCT = randomized controlled trial; SBP = systolic blood pressure; SPAF = Stroke Prevention in Atrial Fibrillation; VA = Veteran Affairs; WHO = World Health Organization; “X”R = effect size.

^b ↑ = statistically significant increased effect; ↓ = statistically significant decreased effect; ↔ = no statistically significant effect.

^c Quality rated as good, fair, or poor based on study design (prospective vs retrospective), likelihood of type 2 error (underpowered analysis due to insufficient patient-years of follow-up, small number of event, or too homogeneous a population), reliability of bleeding definition (use of a well-defined and accepted definition).

^d Number of bleeding events reported.

^e All patients in the group aged ≥ 75 y.

^f All patients in the group aged < 75 y.

^g Only Sundsvall subgroup used for multivariate regression.

^h Only 145 cases and 870 corresponding controls evaluated in multivariate analysis because of missing data.

ⁱ Multivariate regression based on 50 cases of ICH and 200 controls because of incomplete data; 31 cases of intracerebral hemorrhage and 122 controls because of incomplete data.

^j Calculated based on denominator of 565 because outcomes data were lacking for some patients.

^k Results from both the literature and data-based models are reported; history of GIB result taken from the data-based model.

^l Age was analyzed as both continuous and categorical variables.

^m For all patients except 1 patient.

ⁿ Combined intracerebral and subdural hemorrhage patients.

^o Derivation cohort drawn from 565 patients beginning long-term outpatient warfarin therapy.

^p Referent group.

TABLE S5. Evidence Depicting the Association Between Diabetes and Warfarin-Associated Bleeding Risk^a

Reference	Study design	Covariate	Bleeding definition	No. Cases/ Events (Rate/100 PTY)	Univariate P value	Multivariate “X”R (95% CI)	Multivariate P value	Effect (↑ ↔ ↓) ^b	Quality ^c
<i>Major bleeding event</i>									
Lind et al, ³¹ 2009a (N=356)	P, O	Diabetes (n=NR)	Major bleeding events were defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in Hgb level of ≥2 g/dL (≥20 g/L) or leading to transfusion of >2 units (>900 mL) of whole blood.	NR	NS	NA	NA	NA	Poor

Lind et al, ³¹ 2009b (N=356)	P, O	Diabetes (n=NR)	Clinically relevant bleeding was defined as a major or an overt bleeding event based on objective investigations that caused admission to hospital or prolonged hospital care but did not meet the criteria for a major bleeding event	NR	NS	NA	NA	NA	Poor
Manzano-Fernández et al, ²¹ 2009 (N=166)	R, O	Diabetes mellitus (n=88)	A major bleeding event was defined as fatal, decrease in blood Hgb level >4 g/dL, need for transfusion of ≥2 units of blood, need for corrective surgery intervention, the occurrence of intracranial or retroperitoneal bleeding, or any combinations of these events	26 (10.8)	.717	NA	NA	NA	Fair

Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of diabetes mellitus (n=25)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	6 (NR)	0.7	AOR, 1.3 (0.29-7.3)	0.7	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of diabetes mellitus (n=36)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	5 (NR)	0.2	AOR, 4.8 (0.06-362)	0.5	↔	Fair
Poli et al, ²³ 2007 (N=290)	P, O	Diabetes mellitus defined according to ADA criteria (n=57)	Fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal, when surgery or transfusion of >2 blood units were required or when Hgb was reduced by ≥2 g/dL	17 (2.1)	0.09	AOR, 4.4 (1.3-14.7)	0.01	↑	Good
Suzuki et al, ³⁴ 2007 (N=667)	R, O	Diabetes mellitus (n=93)	Bleeding requiring emergent hospitalization and ICHs	12 (2.4)	0.57	AOR, 0.53 (0.06-4.37)	NS	↔	Poor

Wallvik et al, ³⁵ 2007 (N=1579) ^f	P, O	Diabetes mellitus (n=313)	Bleeding event causing admission or prolonged in-hospital care and all fatal bleeding events	114 (NR)	NA	AOR, 0.8 (0.5-1.3)	NS	↔	Good
Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Diabetes (n=31,270) Without complications (n=NR) With complications (n=NR)	Hemorrhagic events were considered <i>serious</i> if the <i>ICD-9-CM</i> code was the primary diagnosis from a VA hospitalization	2546 ^g (1.9)	NR	AHR, 1.05 (0.96-1.15) AHR, 1.03 (0.96-1.10)	NS NS	↔ ↔	Fair
Shireman et al, ³⁶ 2006 (N=19,875)	R, O	Diabetes mellitus (n=5883)	Bleeding defined as GI and intracranial hemorrhages that resulted in an inpatient admission, which were identified by diagnosis-related group codes and <i>ICD-9-CM</i> codes, respectively	318 (NR)	NR	AHR, 1.31 (1.04-1.66)	<.05	↑	Fair
Gasse et al, ¹⁸ 2005 (N=188)	R, O	Diabetes mellitus (n=18)	Bleeding events resulting in hospitalization or fatality	45 (NR)	.33	AOR, 1.7 (0.5-6.8)	NS	↔	Poor

Schauer et al, ²⁵ 2005a (N=9345)	R, O	Diabetes mellitus (n=4290)	Inpatient hospitalization for ICH using <i>ICD-9-CM</i> codes	158 ^g (0.8)	NS	NA	NA	NA	Fair
Schauer et al, ²⁵ 2005b (N=9345)	R, O	Diabetes mellitus (n=4290)	GI bleeding requiring hospitalization using <i>ICD-9-CM</i> codes	864 ^g (4.6)	NS	AHR 1.03 (0.90-1.18)	NS	↔	Fair
Fang et al, ¹⁷ 2004 (N=1190)	R, O	Diabetes mellitus (n=246)	ICH documented by computed tomography or magnetic resonance imaging	170 (NR)	>.20	NA	NA	NA	Poor
Sam et al, ²⁴ 2004 (N=80)	R, O	Diabetes mellitus defined as a nonfasting blood glucose level of 200 mg/dL or use of insulin or an oral hypoglycemic agent (n=13)	Bleeding event resulting in death, hospitalization, or a decrease in Hgb \geq 2 g/dL or requiring \geq 2 units of RBC transfusion	16 (NR)	NS	NR	NS	↔	Poor
Berwaerts & Webster, ¹⁶ 2000a (N=272)	R, O	Diabetes mellitus (n=42)	ICH	68 (NR)	NS	AOR, 0.36 (0.10-1.32) ^h	NS	↔	Fair
Berwaerts & Webster, ¹⁶ 2000b (N=168)	R, O	Diabetes mellitus (n=30)	Intracerebral hemorrhage	42 (NR)	NS	AOR, 0.39 (0.08-1.93) ^h	NS	↔	Fair
McMahan et	R, O	Diabetes	Bleeding event in	40 ^g (5.9)	.27	NA	NA	NA	Poor

al,³² 1998
(N=579)

mellitus
(n=150)

outpatients that
(1) was fatal, (2)
was life-
threatening (led
to cardiopulmo-
nary arrest,
surgical or
angiographic
intervention to
stop the blood
loss, or
irreversible
damage, such as
MI, stroke,
blindness, or
fibrothorax), (3)
was potentially
life-threatening
(led to 2 of 3
consequences:
severe blood loss,
hypotension
[SBP <90 mm
Hg), and critical
anemia with a
hematocrit ≤ 0.2),
(4) led to severe
blood loss (≥ 3
units of blood),
(5) led to surgical
treatment, or (6)
led to moderate
blood loss that
was acute or
subacute, and
was not

			explained by trauma or surgery						
SPAF, 1996 (N=555)	RCT	Diabetes (n=78)	A bleeding event was called major when it involved the central nervous system; required hospitalization, blood transfusion, and/or surgical intervention; or resulted in permanent functional impairment to any degree	33 ^g (2.3)	.09	NA	NA	NA	Poor
Hylek & Singer, ¹⁹ 1994a (N=308)	R, O	Diabetes mellitus (n=52)	Intracerebral hemorrhage	77 (NR)	NS	NA	NA	NA	Poor
Hylek & Singer, ¹⁹ 1994b (N=176)	R, O	Diabetes mellitus (n=27)	Subdural hemorrhage	44 (NR)	NS	NA	NA	NA	Poor

Fihn et al, ²⁹ 1993 (N=928)	R, O	Diabetes mellitus (n=NR)	Serious bleeding defined as bleeding requiring treatment or medical evaluation. Examples of serious bleeding included overt GIB, occult GIB if endoscopic or radiographic studies were done, gross hematuria that prompted cystoscopy or intravenous urography or lasted >2 d, and hemoptysis. If blood was transfused, ≤ 2 units were given	147 [§] (7.5)	NS	NA	NA	NA	Poor
Petitti et al, ²² 1989 (N=2029)	R, O	Treated diabetes mellitus (n=75)	Bleeding event resulting in death or hospitalization	134 (NR)	NS	AHR, 1.1 (0.6- 2.5)	NS	\leftrightarrow	Fair
Minor bleeding events									

Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of diabetes mellitus (n=25)	Bleeding event not requiring hospital admission, emergency procedure, or blood transfusion or having no other medical consequences	47 (NR)	0.6	AOR, 0.35 (0.09-1.4)	0.1	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of diabetes mellitus (n=36)	Bleeding event not requiring hospital admission, emergency procedure, or blood transfusion, or having no other medical consequences	42 (NR)	0.3	AOR, 0.6 (0.19-1.9)	0.4	↔	Fair
Petitti et al, ²² 1989 (N=2029)	R, O	Treated diabetes mellitus (n=75)	Bleeding event not resulting in death or hospitalization	481 (NR)	NS	AHR, 0.6 (0.3-1.1)	NS	↔	Fair

Any Bleeding

Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of diabetes mellitus (n=25)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion and a minor bleeding event was defined as all other bleeding events with no medical consequences	53 (NR)	.40	AOR, 0.3 (0.08-1.2)	.09	↔	Fair
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Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of diabetes mellitus (n=36)	Combination of major and minor bleeding events where a major bleeding event was defined as a bleeding event requiring hospital admission, emergency procedure, and/or blood transfusion and a minor bleeding event was defined as all other bleeding with no medical consequences	47 (NR)	.50	AOR, 0.77 (0.27-2.2)	.60	↔	Fair
Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Diabetes (n=31,270) Without complications (n=NR) With complications (n=NR)	The presence of a hemorrhagic event was based on the presence of specific <i>ICD-9-CM</i> codes indicative of a bleed	10,249 (7.7)	NR	AHR, 1.08 (1.03-1.13) AHR, 1.12 (1.09-1.16)	<.05 <.05	↑ ↑	Fair

^a ADA = American Diabetes Association; AHR=adjusted hazard ratio; AOR = adjusted odds ratio; CI = confidence interval; GI = gastrointestinal; GIB = GI bleeding; Hgb = hemoglobin; *ICD-9-CM* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICH=intracranial hemorrhage; MI=myocardial infarction; NA=not applicable; NR = not reported; NS = not significant; O = observational study; P = prospective; PTY =patient-years; R = retrospective; RBC = red blood cell; RCT =randomized controlled trial; SB P= systolic blood pressure; SPAF = Stroke Prevention in Atrial Fibrillation; VA = Veterans Affairs; “X”R = effect size.

^b ↑=statistically significant increased effect; ↓=statistically significant decreased effect; ↔=no statistically significant effect.

^c Quality rated as good, fair, or poor based on study design (prospective vs retrospective), likelihood of type 2 error (underpowered analysis due to insufficient patient-years of follow-up, small number of events, or too homogeneous a population), reliability of bleeding definition (use of a well-defined and accepted definition).

^d All patients in the group aged ≥ 75 y.

^e All patients in the group aged < 75 y.

^f Only Sundsvall subgroup used for multivariate regression.

^g Number of bleeding events reported.

^h Multivariate regression based on 50 cases of ICH and 200 controls because of incomplete data; 31 cases of intracerebral hemorrhage and 122 controls because of incomplete data.

TABLE S6. Evidence Depicting the Association Between Prior Stroke/TIA (CVD) and Warfarin-Associated Bleeding Risk^a

Reference	Study design	Covariate	Bleeding definition	No. of cases/ events (Rate/100 PTY)	Univariate <i>P</i> -value	Multivariate “X”R (95% CI)	Multivariate <i>P</i> value	Effect (↑ ↔ ↓) ^b	Quality ^c
<i>Major bleeding event</i>									
Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of ischemic cerebrovascular stroke (n=60)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	6 (NR)	.50	AOR, 0.54 (0.02-11.8)	.70	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of ischemic cerebrovascular stroke (n=38)	Bleeding requiring hospital admission, emergency procedure, and/or blood transfusion	5 (NR)	.30	AOR, 15.9 (0.19-135)	.20	↔	Fair

Poli et al, ²³ 2007 (N=290)	P, O	Stroke defined rapidly developing clinical symptoms and/or signs of focal and at times global loss of brain function, lasting >24 hours, and with no apparent cause other than vascular; or TIA defined as a neurological defect lasting <24 hours (n=111)	Fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal, when surgery or transfusion of >2 blood units (>900 mL) were required or when Hgb was reduced by ≥ 2 g/dL (20 g/L)	17 (2.1)	.01	AOR, 3.6 (1.1-11.6)	.03	↑	Good
Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Stroke (n=12,556)	Hemorrhagic events were considered "serious" if the <i>ICD-9-CM</i> code was the primary diagnosis from a VA hospitalization	2546 ^f (1.9)	NR	AHR, 1.25 (1.14-1.38)	<.05	↑	Fair

Fang et al, ¹⁷ 2004 (N=1190)	R, O	History of cerebrovascular disease defined as previous ischemic stroke or carotid artery disease (n=267)	ICH documented by computed tomography or magnetic resonance imaging	170 (NR)	<.001	AOR, 2.2 (1.4-3.4) ^g	<.05	↑	Fair
Sam et al, ²⁴ 2004 (N=80)	R, O	Stroke (n=19)	Bleeding resulting in death, hospitalization, or a decrease in Hgb ≥ 2 g/dL or requiring ≥ 2 units of RBC transfusion	16 (NR)	NS	NA	NA	NA	Poor
Ruiz-Irastorza et al, ⁵¹ 2002 (N=66)	R, O	Previous stroke (n=38)	Defined as intracranial, intraocular, GI, retroperitoneal, or requiring transfusion or admission to a hospital, were considered for the purposes of this study	4 (6)	NS	NR	NS	↔	Poor
Berwaerts & Webster, ¹⁶ 2000a (N=272)	R, O	Cerebrovascular disease (n=81)	ICH	68 (NR)	<.05	AOR, 2.32 (0.98-5.46) ^h	NS	↔	Poor
Berwaerts & Webster, ¹⁶ 2000b (N=168)	R, O	Cerebrovascular disease (n=47)	Intracerebral hemorrhage	42 (NR)	<.05	AOR, 3.01 (0.97-9.40) ^h	NS	↔	Poor

White et al, ⁵⁵ 1999 (N=21,250)	R, O	Prior stroke (n=1317)	Patients were categorized as having a hospital readmission for bleeding if the principal diagnosis was site-specific bleeding, system-specific bleeding, nonspecific hemorrhage, or prolonged blood clotting with a secondary diagnosis of a site- or system-specific bleeding code. A readmission was also included if the principal diagnosis was a potential source of bleeding with a secondary diagnosis bleeding	298 (0.9)	.30	NA	NA	NA	Fair
McMahan et al, ³² 1998 (N=579)	R, O	Stroke (n=74)	Bleeding in outpatients that (1) was fatal, (2) was life-threatening (led to cardiopulmonary arrest, surgical or	40 [†] (5.9)	.71	AHR, 1.2 (0.50-2.9) ^{ij}	.68	↔	Fair

angiographic
intervention to
stop the blood
loss, or
irreversible
damage, such as
MI, stroke,
blindness, or
fibrothorax), (3)
was potentially
life-threatening
(led to 2 of 3
consequences:
severe blood loss,
hypotension (SBP
<90 mm Hg), and
critical anemia
with a hematocrit
≤0.2), (4) led to
severe blood loss
(≥3 units of
blood), (5) led to
surgical
treatment, or (6)
led to moderate
blood loss that
was acute or
subacute, and was
not explained by
trauma or surgery

Gitter et al, ³⁰ 1995 (N=261)	R, O	TIA (n=40)	Classified as a major bleeding event based on bleeding severity index determined independently by 2 physicians	18 (8.1)	NS	NR	NS	↔	Poor
Gitter et al, ³⁰ 1995 (N=261)	R, O	Stroke (n=49)	Classified as a major bleeding event based on bleeding severity index determined independently by 2 physicians	18 (8.1)	NS	NR	NS	↔	Poor
Hylek & Singer, ¹⁹ 1994a (N=308)	R, O	Cerebrovas- cular disease defined as carotid/ vertebro- basilar disease, or history of stroke (n=125)	Intracerebral hemorrhage	77 (NR)	<.05	AOR, 3.1 (1.7- 5.6)	<.001	↑	Fair
Hylek & Singer, ¹⁹ 1994b (N=176)	R, O	Cerebrovas- cular disease defined as carotid/ vertebro- basilar disease, or history of stroke (n=58)	Subdural hemorrhage	44 (NR)	NS	NA	NA	NA	Poor

Hylek & Singer, ¹⁹ 1994c (N=484)	R, O	Cerebrovascular disease defined as carotid/vertebro-basilar disease, or history of stroke (n=183)	Intracranial hemorrhage documented by computed tomography, lumbar puncture, or postmortem examination ^k	121 ^c (0.6)	NR	AOR, 2.3 (1.4-3.7)	<.001	↑	Fair
Landefeld & Goldman, ²⁰ 1989 (N=375) ^l	R, O	Current or past stroke (n=4)	Bleeding in outpatients that (1) was fatal, (2) was life-threatening (led to cardiopulmonary arrest, surgical or angiographic intervention to stop the blood loss, or irreversible damage, such as MI, stroke, blindness, or fibrothorax), (3) was potentially life-threatening (led to 2 of 3 consequences: severe blood loss, hypotension (SBP <90 mm Hg), and critical anemia with a hematocrit ≤0.2), (4) led to	NR (NR)	<0.01	AHR, 1.69 (NR)	<.01	↑	Fair

severe blood loss (≥3 units of blood), (5) led to surgical treatment, or (6) led to moderate blood loss that was acute or subacute, and was not explained by trauma or surgery

Minor bleeding event

Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of ischemic cerebrovascular stroke (n=60)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical consequences	47 (NR)	.60	AOR, 2.2 (0.86-5.6)	.10	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of ischemic cerebrovascular stroke (n=38)	Bleeding not requiring hospital admission, emergency procedure, blood transfusion, or with no other medical consequences	42 (NR)	.90	AOR, 0.54 (0.17-1.7)	.30	↔	Fair

Any Bleeding

Poli et al, ³³ 2009 (N=783)	P, O	Stroke/TIA (n=229)	Combination of major and minor bleeding events where a major bleeding event was defined as fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; when surgery or transfusion >2 blood units were required or when Hgb was ≥ 2 g/dL; a minor bleeding event was defined as all cases of bleeding not categorized as major	94 (3.7)	.007	NA	NA	NA	Fair
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Abdelhafiz & Wheeldon, ¹⁵ 2008a (N=199) ^d	P, O	History of ischemic cerebrovascular stroke (n=60)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	53 (NR)	.80	AOR, 2.1 (0.84-5.1)	.10	↔	Fair
Abdelhafiz & Wheeldon, ¹⁵ 2008b (N=203) ^e	P, O	History of ischemic cerebrovascular stroke (n=38)	Combination of major and minor bleeding events where a major bleeding event was defined as bleeding requiring hospital admission, emergency procedure, and/or blood transfusion; a minor bleeding event was defined as all other bleeding with no medical consequences	47 (NR)	.70	AOR, 0.71 (0.24-1.9)	.50	↔	Fair

Berlowitz et al, ²⁷ 2006 (N=66,988)	R, O	Stroke (n=12,556)	The presence of a hemorrhagic event was based on the presence of specific <i>ICD-9-CM</i> codes indicative of a bleed	10,249 ^f (7.7)	NR	AHR 1.12 (1.07-1.17)	<.05	↑	Fair
Gitter et al, ³⁰ 1995 (N=261)	R, O	TIA (n=40)	Classified as major or minor bleeding event based on bleeding severity index determined independently by 2 physicians	27 (12.2)	NS	NR	NS	↔	Poor
Gitter et al, ³⁰ 1995 (N=261)	R, O	Stroke (n=49)	Classified as major or minor bleeding event based on bleeding severity index determined independently by 2 physicians	27 (12.2)	NS	NR	NS	↔	Poor

^a AOR = adjusted odds ratio; CI = confidence interval; GI = gastrointestinal; Hgb = hemoglobin; AHR = adjusted hazard ratio; *ICD-9-CM* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICH = intracranial hemorrhage; NA = not available; NR = not reported; NS = not significant; O = observational study; AOR = odds ratio; P = prospective; PTY = patient-years; R = retrospective; RBC = red blood cell; SBP = systolic blood pressure; TIA = transient ischemic attack; VA = Veteran Affairs; “X”R = effect size.

^b ↑=statistically significant increased effect; ↓=statistically significant decreased effect; ↔=no statistically significant effect.

^c Quality rated as good, fair, or poor based on study design (prospective vs retrospective), likelihood of type 2 error (underpowered analysis due to insufficient patient-years of follow-up, small number of events, or too homogeneous a population), reliability of bleeding definition (use of a well-defined and accepted definition).

^d All patients in the group aged ≥75 y.

^eAll patients in the group aged <75 y.

^fNumber of bleeding events reported.

^gOnly 145 cases and 870 corresponding controls evaluated in multivariate analysis because of missing data.

^hMultivariate regression based on 50 cases of ICH and 200 controls because of incomplete data; 31 cases of intracerebral hemorrhage and 122 controls because of incomplete data.

ⁱCalculated using a denominator of 565 because outcomes data were lacking for some patients.

^jResults from both the literature and data-based models are reported; history of GI bleeding result taken from the data-based model.

^kFor all except 1 patient.

^lDerivation cohort drawn from 565 patients beginning long-term outpatient warfarin therapy.

TABLE S7. Evidence Depicting the Association Between CHADS₂ Score and Warfarin-Associated Bleeding Risk

Reference	Study design	Covariate	Bleeding definition	No. of cases/ events (rate/100 PTY)	Univariate <i>P</i> value	Multivariate “X”R (95% CI)	Multivariate <i>P</i> value	Effect (↑ ↔ ↓) ^b	Quality ^c
<i>Any Bleeding</i>									
Poli et al, ³³ 2009 (N=783)	P, O	Linear CHADS ₂ score per point	Combination of major and minor bleeding events where a major bleeding event was defined as fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; when surgery or transfusion >2 blood units (>900 mL) were required or when Hgb was ≥2 g/dL (≥20 g/L); a minor bleeding event was defined as all cases of bleeding not categorized as major	94 (3.7)	0.03	NA	NA	NA	Fair

^a CHADS₂ = chronic heart failure, hypertension, advanced age, diabetes, and prior stroke/transient ischemic attack; CI = confidence interval; Hgb = hemoglobin; NA = not available; O = observational study; P = prospective; PTY = patient-years; “X”R = effect size.

^b ↑ = statistically significant increased effect; ↓ = statistically significant decreased effect; ↔ = no statistically significant effect.

^c Quality rated as good, fair, or poor based on study design (prospective vs retrospective), likelihood of type 2 error (underpowered analysis due to insufficient PTY of follow-up, small number of events, or too homogeneous a population), reliability of bleeding definition (use of a well-defined and accepted definition).